









**DILLING'S**  
**CLINICAL PHARMACOLOGY**



# DILLING'S CLINICAL PHARMACOLOGY

TWENTIETH EDITION

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## PREFACE

can medical practice be safeguarded from uninspired empiricism and from the stultifying effects of authoritarianism.

In teaching pharmacology to medical students it is clearly possible (and indeed desirable) to correlate it to other subjects in the curriculum. Thus senior students in the Physiology course are well equipped to grasp quickly the principles of pharmacology. Again, when students have left the physiology department they welcome a presentation of pharmacology which has a distinct clinical flavour. At the stage when advanced students are personally concerned with drawing up schemes of treatment for individual patients, they benefit from didactic instruction in therapeutics; and as this subject embraces drug therapy there should be no difficulty in recognising the importance of "applied pharmacology" to the medical practitioner. This sequential policy in relation to teaching is as obvious in the design of the medical curriculum as it is in other curricula, but in practice the method succeeds only insofar as the student is willing to recognise it and take advantage of it.

Dilling's *Pharmacology* has been re-written with the intention of giving the greatest emphasis to the subject in its bearing on the practice of medicine. The book in its present form is intended to bridge the gap which often exists between Experimental Pharmacology in its academic setting and Medical Treatment—where attention is properly directed mainly to the *results* of drug therapy rather than to the rationale for the use of drugs in the plan of treatment. The contributors have been particularly concerned to bring out general principles of pharmacology which are important in the daily work of the clinical student and the medical practitioner. Indeed, unless a teacher of pharmacology in its clinical aspects is committed to sheer empiricism he must constantly look for such principles; and this method of teaching and learning remains unassailable even though, in the light of increasing knowledge, long established views must give place to new ones. Thus many clinicians have tried to teach the actions of digitalis on the basis of the theory of a *circus movement* of the cardiac impulse, but this concept is now rarely mentioned except as a matter of historical interest. Again the sympathomimetic action of ephedrine is usually explained in terms of its capacity to inhibit the action

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of amine oxidase, but it now seems that this attractive concept of a pharmacological mechanism is untenable in its present form.

When dealing with the subjects included in a textbook of this kind, it is doubtful whether there is any substantial advantage in adhering closely to a particular scheme of presentation. An attempt has been made to offer a readable account of the material under review, and some conventional methods have consequently been abandoned. Pharmaceutical details have been eliminated from the text, and the topics under consideration are generally illustrated by referring to a limited number of preparations in common use. At the same time, when drugs of major importance are dealt with, certain cardinal features of clinical pharmacology recur almost invariably. These, in their usual order of appearance in the text are as follows. The sources of the drug are mentioned, and reference may be made to chemical composition either in the text or in the Formulary; the pharmacological actions are then mentioned with emphasis on those which have therapeutic applications, and side-effects and toxic effects are correlated if possible to pharmacological actions; and finally the therapeutic uses of the drug are considered, and attention is drawn to the most appropriate preparations and methods of administration. It is obvious that certain drugs (for example, ferrous sulphate, morphine hydrochloride, digitalis, etc.) are prototypes which have become standard remedies against which others are assessed. In this book, therefore, drugs which can be regarded as "standard" receive full consideration on the lines indicated, whereas other drugs are discussed more briefly.

Additional information, taken from books of reference (pharmacopœias, formularies, etc.), appears as an Appendix—where the sections are numbered to correspond with the chapters of the book. Here again only a few of the available preparations are mentioned, the choice being determined mainly by what the clinician is likely to need in practice. It is assumed that clinical students and practitioners will have access to standard works of reference such as the *British Pharmaceutical Codex* and *The Extra Pharmacopœia* (Martindale) Vol. I. where details are readily available about a wide range of pharmaceutical preparations.

I am indebted to the staff of the Department of Materia Medica



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and Therapeutics based at Stobhill General Hospital, Glasgow, for their substantial contributions to this textbook in its present form. Dr. J. G. Macarthur and Dr. T. J. Thomson have rendered additional help in sharing the editorial responsibility of criticising draft manuscript and preparing material for the Publisher; and Dr. Denney Smith has supervised the collection of data for the Formulary (Appendix II). Mr. John J. Lewis, Senior Lecturer in Experimental Pharmacology, kindly co-operated with me in writing Chapter 1.

I am grateful to Dr. Bernard Isaacs, a former member of my department, who was responsible for many useful developments in the teaching of practical pharmacy and practical pharmacology set out in Appendix III. Mr. David Blackwood, Chief Pharmacist at Stobhill General Hospital, Glasgow, kindly checked the section on the Dangerous Drugs Act and the pharmaceutical aspects of prescribing.

Dr. Michael Martin-Smith has contributed an extensive survey of the subject described as Pharmaceutical Chemistry: Nomenclature of Drugs (Appendix IV). The ability to understand the intricacies of chemical nomenclature in relation to pharmacology necessarily depends on the student's basic knowledge of chemistry and biochemistry. It follows that junior clinical students, fresh from the science departments, are most favourably placed to read this subject profitably. Much of this Appendix is to be regarded as material for reference only; but the general principles and the examples should be studied with special care by all clinical students. Mr. Callander, medical artist in the University of Glasgow, prepared the chemical formulæ for publication.

A great deal of exacting work has devolved upon my secretaries Miss E. J. Newell and Miss J. S. Hutton: I am exceedingly grateful to them for their skill and for their unfailing helpfulness. Miss M. Paton, working in the library, prepared the short bibliography (Appendix V).

Messrs. Cassell and Company Ltd. have displayed that forbearance which has become a tradition among publishers of medical textbooks, and the Firm has earned the gratitude of all who have contributed to the re-writing of Dilling's manual.

S. A.

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# CHAPTER 1

## INTRODUCTION

It is justifiable to take a broad view of the doctor's responsibilities when he assumes professional charge of a patient (Lat. *patior*--I suffer). A great many forms of treatment are available, but they are all embraced by the word *therapeutics* -- meaning to care for, to tend and to nurse. Therapeutics may therefore be defined as that branch of medicine which is concerned with the cure of disease and the relief of suffering. Thus, due emphasis is given to the fact that much of a medical practitioner's time is spent in trying to alleviate the *effects* of disease, as there is a wide range of disabilities for which no specific remedies are available. Physicians and surgeons often resort to the use of drugs and many other substances and materials to promote therapeutic objectives. Broadly speaking, all these substances belong to the *materia medica*. The meaning attached to the term "materia medica" depends largely on tradition in the individual medical schools, but it should not be confused with *pharmacy* and still less with *pharmacology*. On a narrow interpretation, the term *materia medica* is applied to the materials or substances used in Medicine, their names, sources, physical characters and chemical properties, the preparations made from them, and the dose in which they may be given. The definition properly focuses attention mainly on drugs, biological products and diagnostic agents; and a *drug* is any substance other than a food used in medical treatment.

PHARMACOLOGY or pharmacodynamics defines the mode of action of drugs on living animals, organs or tissues; the physiologist and the pharmacologist necessarily speak the same language, for the action of drugs can be described only by comparison with normal reactions. A drug may increase or decrease the activity of a cell, but it cannot confer on the cell any *new* functions; in other words, changes if they occur are quantitative, never qualitative. One special development of pharmacology--*chemotherapy*--is concerned with the effect of drugs upon micro-



organisms and parasites living and multiplying in a patient's tissues. Nearly all these substances are synthetic compounds which are selectively toxic for the micro-organisms, yet having little or no adverse effects on the host.

When the investigation of the action of drugs is carried out on man—as distinct from laboratory animals—the discipline of study is called *human pharmacology* or *applied pharmacology*, and it can be regarded as a part of experimental medicine—which in turn belongs to *clinical science*. This book is concerned almost exclusively with pharmacological actions in man and with providing an account of how drugs are used in the practice of therapeutics. Such emphasis seems reasonable in a manual for students whose training is conducted mainly at the patient's bedside and in the outpatient department. It must not be forgotten, however, that physiology and general pharmacology are the foundations on which human pharmacology is built.

PHARMACY is the name given to the art of making and formulating suitable preparations of drugs used by the medical practitioner. Manufacturing pharmacists now provide not only the drugs listed individually in the pharmacopœias of the world, but also the new and non-official remedies and a wide range of preparations containing drugs conveniently compounded for specified therapeutic uses. Retail pharmacists work largely as distributors of ready-made preparations. There are obvious advantages in developments on these lines. Almost inevitably, however, there has been a steady decline in the doctor's interest in pharmacy and dispensing; and his training in these subjects is now very limited. The deficiency has had serious consequences, because an elementary knowledge of pharmacy enables the practitioner to prescribe more intelligently; and it is likely to make him more critical in his assessment of new drugs and new preparations of old drugs. A short account of pharmaceutical terms is given in Appendix I.

*Pharmaceutical chemistry* is concerned with the structure of active principles which are used as drugs—either synthetic or occurring in nature.

*Pharmacognosy* is the knowledge of the botanical features of medicinal plants, the microscopical characters of sections and of powders made from their useful portions; in commerce the

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pharmacognosist must also be familiar with adulterants. This subject now lies entirely within the province of a small number of pharmaceutical specialists. Medical students are no longer expected to profess any knowledge of pharmacognosy. Nevertheless, a few still aspire to distinguish at a glance between, say, a castor-oil seed and a Calabar bean, or between baking soda and washing soda. A physician who is not excessively ignorant of such matters will at least be able to consult books of reference profitably; and he may expect to acquit himself with credit in exchanges with the Coroner or the Procurator Fiscal.

## PHARMACOPŒIAS

During historical times an enormous number of drugs have been used and there is a correspondingly extensive literature. Very few of these drugs have been retained as valuable therapeutic agents; the fate of the vast majority tells a story of hopes unfulfilled, and incidentally reveals that through the centuries the credulity of mankind has been matched by the ingenuity of the opportunist and the persuasiveness of the charlatan. Even as recently as the 18th century formularies were little more than lists of drugs apparently chosen at random or with no more authority than that provided by folk-lore. These strange conglomerations revealed the physician's weakness for the bizarre and the occult; and his approach to medicine seemed designed to perplex rather than to enlighten the intelligent patient. Both pharmacist and physician were seriously hampered by their limited knowledge of chemistry, physics and biology. They were handicapped still further by their reluctance to incorporate into the practice of medicine the elementary principles of logic and the criteria demanded by the experimental physiologist—notwithstanding the guidance offered by such men as William Harvey and Stephen Hales. Nevertheless, medicine today is indebted to a number of empirical but critical practitioners of the past: drugs such as iron and quinine were in use hundreds of years before their effects were investigated by pharmacologists, and the medicinal virtues of opium were recorded more than 2,000 years ago. The information thus made available was empirical and called for systematisation, but it was nevertheless invaluable for the medical

practitioner. As pharmaceutical chemistry developed out of physics and general chemistry in the second half of the 19th century, lists of drugs were prepared by the joint enterprise of pharmacists and physicians in nearly all civilised countries. Their purpose was to provide an authoritative description of drugs in current use, to list their preparations and state their recommended doses.

Some of these books are now standard works of reference, such as the *British Pharmacopœia* (BP), the *United States Pharmacopœia* (USP) and the *International Pharmacopœia* (IP). They are revised by standing committees of experts, and new editions are published every five years. As far as it is reasonably possible, the BP is kept up to date by the publication of a supplement called an Addendum in the third year of the "life" of the current edition. Drugs and their preparations listed in the BP are said to be "official". This description serves to remind the doctor and the pharmacist that the BP is published by the General Medical Council, which in turn derives its authority from the Privy Council. In the United Kingdom and in the British Commonwealth its status is unique.

*The British Pharmaceutical Codex* is published by the Council of the Pharmaceutical Society of Great Britain. It describes not only all the principal official preparations listed in the BP, USP and other contemporary pharmacopœias, but also a number of compounds which are not official. Its value as a book of reference is greatly enhanced by the inclusion of concise accounts of the actions and uses of the drugs described.

*The Extra Pharmacopœia* (now in its 23rd edition) was first produced by William Martindale, but is now published by the Council of the Pharmaceutical Society. It has become a classic work of reference for the medical practitioner and the pharmacist and also for laboratory workers. Volume I is of particular interest to the physician as it contains the factual data of current pharmacopœias, notes on old and new drugs which are not official, and details about many trade preparations. There are also abstracts of selected medical literature relating to pharmacology and therapeutics, and monographs on groups of substances such as the sulphonamides and antibiotics. Other sections contain summaries of

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poisons legislation and the Dangerous Drugs Act; and among other topics, biological products, blood transfusion and surgical ligatures receive attention.

*British National Formulary.* Some ailments are very common, and so far as *prescribing* is concerned their treatment is often stereotyped. In the past many hospitals, recognising this, drew up their own formularies usually pocket-books listing stock mixtures, tablets, ointments and other preparations in common use. The practice had obvious advantages for prescriber and dispenser. During the Second World War a *National War Formulary* (NWF) was brought into use in Britain. It was a list of drugs in wide demand, but selected with some regard to reducing the importation of drugs from abroad. Subsequently the NWF became the NF and is now called the *British National Formulary* (BNF). In addition to listing simple prescriptions from which a choice can be made, the BNF contains useful "Notes for Prescribers" in which the indications for therapy are discussed and the merits of different preparations are examined. As a prescriber's guide the BNF is the most valuable book of its kind for practitioners and students in the United Kingdom.

A short bibliography of British and American books of reference is given on p. 843. It is important that the student should be acquainted with the scope of these works and that he should acquire the habit of consulting them on matters of detail which cannot be included in ordinary textbooks.

## PRINCIPLES OF PRESCRIBING

If the scheme of treatment includes the use of drugs, the doctor normally communicates with the pharmacist. This "communication" necessarily precedes the dispensing of the medicine: it is therefore called a *prescription*. A prescription has no intrinsic merit: it is a written statement indicating a form of drug therapy, and it carries with it the presumption that in the doctor's opinion such treatment is appropriate to the needs of a particular patient. When a prescription is written it should be regarded as the logical sequel to diagnosis and the outcome of a comprehensive assessment of the patient's requirements. In other words, the first step in treatment is *diagnosis*; and no pharmaceutical preparation, how-

ever elegant, can compensate for an inadequate understanding of the nature of the patient's illness.

Prescription writing is not an occult science. A great disservice has been done in the past by those who have tried in various ways to enshroud the subject in mystery. A communication from the doctor to the pharmacist should be simple and unambiguous. In Britain a prescription should be written in plain English—either in full or correctly abbreviated. The use of Dog-Latin has nothing to commend it. A prescription should be easily legible. In some countries a doctor who writes illegible prescriptions is liable to serious penalties, including imprisonment. There are physicians who protest that if prescriptions were written legibly and in English they might be read by patients. It is difficult to understand why this should be regarded as a disadvantage; if a patient's education permits of his taking an intelligent interest in the treatment he is receiving, so much the better. On the other hand, if it is important that the patient should be kept in ignorance of the nature of the drugs which he is receiving, the prescription should not be made available to him; it should be conveyed to the pharmacist by post or by messenger. In practice the need for this is an extremely rare occurrence.

Before he begins to write a prescription the doctor must be able to give satisfactory answers to the following questions: What is the diagnosis? Is a specific remedy available for this disease? Is this an occasion when it is justifiable to give drugs which merely relieve symptoms? (In many diseases symptomatic relief is indeed all that can be achieved by drug therapy, but the value of such treatment is often very great.) Can the desired pharmacological action be produced by using a pharmaceutical preparation listed in the BPC or in the BNF? In practice the experienced doctor covers this ground rapidly. Further, he is often faced by the need to plan and supervise the treatment on the basis of bedside diagnosis in order to cope expeditiously with the presenting disability (pyelonephritis, pneumonia, cardiac failure, gout, etc.), leaving detailed study of his case notes and further therapeutic refinements until a few days or a few weeks have elapsed. As for the prescription itself, let it be supposed that a patient seeks treatment for tapeworm infestation and the diagnosis is confirmed

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by the doctor. He may reasonably decide to give the patient mepacrine in an attempt to get rid of the worm. On a prescription form he enters the patient's name and address. He then writes the words *Mepacrine hydrochloride* and its dose, 0.1 G., in the centre of the page. Below this he adds his request to the pharmacist—“*Send ten tablets*” and the further request to the pharmacist—“*Label: the tablets as directed*”. The doctor then adds his signature and the date, and the communication to the pharmacist is complete (see also p. 637).

In Appendix III a number of prescriptions are set out to show the format adopted for convenience. Before a drug is mentioned it is commonly preceded by the sign **R** which stands for *Recipe*—meaning “*Take thou*”—recalling that in writing a prescription the doctor is in fact addressing the pharmacist and asking him to take the drugs listed and compound them in suitable fashion. The stroke across the tail of the letter R is said to have been introduced as an invocation to Jupiter to make the medicine effective. The modern doctor—who looks to physiology rather than mythology—may well decide to omit the sign altogether.

The medical profession is well served by the pharmaceutical industry: individual drugs and compound preparations of drugs listed in the BP, BPC and BNF are all readily available to the prescriber; and in the various technical processes involved, manufacturers adhere to the exacting standards laid down by the BP Commission. Not surprisingly, experience shows that it is only on rare occasions that the doctor needs to prescribe pharmaceutical preparations other than those which are official. One of the most fertile causes of uncritical treatment and injudicious prescribing is the doctor's failure to use his books of reference. In this matter he has much to learn from the scientist and the lawyer who constantly check their decisions by resorting to standard works. There is nothing new in this procedure: it is merely part of the technique of education and inquiry accepted by members of the learned professions. It is abandoned only at the cost of forfeiting the right to exercise personal judgment. Thus instead of determining the needs of the individual patient and deciding whether these can be met through the application of pharmacological principles, the doctor may drift into the habit of prescribing according to the

dictates of fashion. It is imperative that the student should acquire the habit of reviewing the whole range of pharmaceutical preparations offered for a specified therapeutic purpose—for example, the suppression of cough, the treatment of peptic ulcer, the management of hay fever, etc. Such exercises will be part of his professional responsibility during his whole working life.

It has been emphasised that, in the approach to prescribing, the student and the doctor are obliged to think first of the broad pharmacological principles which are appropriate to the circumstances. When decisions have been made, it is still necessary to choose a suitable pharmaceutical preparation of the drug or drugs which are to be given. A working knowledge of these preparations is best acquired by close and critical study of what is being prescribed in the hospital wards; and the value of this practical work is greatly enhanced by constant use of textbooks and works of reference. Almost by definition, reference books are comprehensive; but it is equally true that they are designed for occasional use and not for systematic reading. Martindale's *Extra Pharmacopæia* is such a book: it is obviously a companion volume to the standard textbooks of materia medica, pharmacology and therapeutics. Are the needs of the patient being fully met by prescribing official preparations? If not, what are the names of the non-official preparations which may prove therapeutically superior? These questions can be answered only by resorting to books of reference. The need for such help is apparent when it is recalled that there are upwards of ten thousand proprietary preparations on the market. One of the modest claims which must be made on behalf of "official" publications such as *The Extra Pharmacopæia* and the BPC is that they act as correctives to the exuberance occasionally displayed in the descriptive literature issued by manufacturers.

For the competent practitioner the task of assessing these proprietary preparations is not as formidable as it would appear to be at first sight. Each of them falls into one or other of a few categories.\* Further details are given on pp. 640-641.

\* The text here is based on the principles of categorisation set out in the leaflet issued by H.M.S.O. in 1954 for the Ministry of Health and the Department of Health for Scotland, entitled—Central Health Services Council and Scottish Health Services Council: *Report of the Joint Committee on Prescribing*.

## INTRODUCTION

A preparation sold under a trade name may be *identical* with the standard preparation.

Again, a preparation may be *similar* to a standard preparation, having been modified quantitatively or qualitatively in a way that does not significantly affect its therapeutic applications.

There are other preparations which, though they are in no way superior therapeutically to standard preparations, are dispensed in an "*elegant*" form—a term which usually implies the generous use of flavourings, exceeding what an unbiased pharmacist would consider essential.

An important but small group consists of *new* substances of proved therapeutic value. Many of these are newly created synthetic compounds designed for specific therapeutic purposes. Such drugs are likely to be accepted by the British Pharmacopœia Commission and to become *official*—by subsequent inclusion in the BP or in an Addendum to the BP.

There is also a large number of pharmaceutical preparations which are *not of proved therapeutic value*. This is not to say that they have necessarily been shown to be useless, but simply that evidence of therapeutic value is still lacking; and it must be emphasised that the onus of proof that a drug is of therapeutic value rests on those who make the claim. Some preparations of this type are offered individually; others are compounded with drugs of proved therapeutic value.

At the present time few doctors in Britain would prescribe scorpions, earthworms or wood-lice. Nevertheless, in the 18th century these were "official" in the sense that they were included in the Pharmacopœia of the Royal College of Physicians of London; and even sweat and human skull-bones have been used therapeutically by intelligent practitioners. To focus attention on the revolting character of many of these old "remedies" is largely to miss the point at issue. The crux of the matter is that far too often the introduction of new medicines has been the outcome of superstition and guesswork rather than the reward of reasoning and experiment.

It cannot be denied that some day the BP may include a preparation derived from earthworms or scorpions. If this materialises it is practically certain (judging from current trends) that official



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status will be earned only on the grounds that such a preparation has been shown, beyond all reasonable doubt, to possess therapeutic effects.

### CLASSIFICATION OF DRUGS

The site of action of a drug can usually be determined with some degree of precision, but it is rarely possible to state—in biochemical terminology—exactly what is occurring in the tissues concerned. Pharmacological and clinical studies have been designed to localise the site of action of drugs and attempts made to analyse the mechanisms underlying the observed effects. At least three systems of classification have thus been evolved:

1. Drugs may be classified according to their site or sites of action. On this basis magnesium sulphate and atropine can be described as acting upon the alimentary system; digitalis and quinidine upon the heart; acetylsalicylic acid upon the central nervous system and acetazolamide upon the kidney.

2. It is also possible to classify these compounds according to their therapeutic effects. Magnesium sulphate is thus a purgative, atropine a spasmolytic and mydriatic, acetylsalicylic acid an analgesic and antipyretic, and acetazolamide a diuretic.

3. The third system of classification, which is based upon the effect of the drug on cellular function is necessarily incomplete as our knowledge in this direction is still very limited. In such a classification we describe atropine as an anticholinergic agent, acetazolamide becomes a carbonic anhydrase inhibitor and magnesium sulphate an osmotic purgative. From the point of view of the medical practitioner the first two systems of classification, though admittedly clumsy and empirical, are the more important. The last is primarily the concern of the laboratory worker, but it represents an approach to pharmacology which will gradually become established among critical practitioners of medicine.

### ADMINISTRATION AND ABSORPTION OF DRUGS

The route of administration of a drug is of primary importance in determining rate and uniformity of absorption. The more rapidly the drug is absorbed the shorter the period of time between administration and onset of systemic effect. When

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absorption proceeds uniformly the effects upon the patient are more readily predictable. Slow, irregular absorption is likely to lead to fluctuating concentrations of the drug in the blood and sharp variations in the intensity of pharmacological action.

The physician's assessment of the needs of the individual patient largely determines the route chosen, but the alternatives open to him are often restricted when he considers the chemical composition of the drug and its fate in the tissues. A preparation of insulin which would be therapeutically satisfactory when taken orally would represent a great advance in the management of the diabetic. Insulin however, is a polypeptide: it is inactivated by enzymes in the digestive juices and it must therefore be injected. For the control of arterial hypertension hexamethonium may be administered by mouth, but absorption is irregular and blood levels therefore fluctuate widely. Stabilisation of the patient's blood pressure by means of this drug is accordingly difficult or impossible, so that oral administration of hexamethonium was abandoned in favour of parenteral therapy; and the search for stable and reliable hypotensive drugs continued. All quaternary salts are strongly ionised when in solution and the cation of hexamethonium is poorly absorbed because it is either repelled from the absorbing surface by receptors carrying like charges or held firmly to the surface by those carrying unlike charges.

**ORAL ADMINISTRATION.** This is undoubtedly the best method if it gives satisfactory results. The patient expects to receive medicines by mouth and is more or less resentful of other methods of administration unless they are unavoidable. When drugs are given orally the patient is spared the hazards of parenteral therapy, and in some circumstances these risks are indeed formidable. On the other hand, many drugs are unpalatable; they may also cause irritation in the gastro-intestinal tract, resulting in nausea, vomiting and diarrhoea. Again, the varying physical and chemical conditions in the alimentary canal may lead to variations in the rate of absorption, but in general this drawback is not conspicuous under clinical conditions. The production of appropriate preparations for oral administration is a matter for the pharmaceutical industry and the careful study devoted to this problem

has overcome many difficulties. Nevertheless there are obvious limitations: if drugs are destroyed in the alimentary canal by the digestive juices or if they cannot produce the desired systemic effect because they are unable to pass through the intestinal mucosa, it is obviously futile to administer such drugs by mouth. The time factor is also important: if an immediate therapeutic effect is imperative, parenteral administration of the drug is indicated—provided that a suitable preparation is available; in the case of the unconscious patient, the injection of the drug parenterally is usually the method of choice.

**PARENTERAL ADMINISTRATION.** When drugs are given by routes other than the alimentary tract (the *enteron*) they are given parenterally—meaning into the body tissues at some level between the skin surface and the wall of the bowel. In practice the clinician restricts the term to the injection of drugs subcutaneously, intramuscularly and intravenously: other extra-alimentary routes of administration include the injection of drugs into joint spaces, serous sacs and the subarachnoid space. When drugs gain access to the blood stream following absorption from the respiratory tract, the genito-urinary tract, the conjunctival sac, etc., it is perhaps best to regard these as special types of “external” administration.

The advantages and disadvantages of parenteral injection and some other modes of administration will now be considered briefly. The techniques used are best learnt by practice in the laboratory and in the wards.

*Subcutaneous Injection.* The drug is dissolved in not more than 2 ml. of sterile water or physiological saline and the solution is injected into the superficial fascia. A small volume of solution that is approximately isotonic causes little discomfort. The rate of onset of the action of a drug given subcutaneously varies with the circumstances: the nature of the drug, local reaction with the tissues, the degree of vascularity at the site of injection and the concentration of the solution (rapidity of absorption is favoured by high concentration). Drugs which irritate the tissues must not be injected subcutaneously as they cause severe pain and there

## INTRODUCTION

may even be necrosis of fascia and skin. Potential irritants are more readily tolerated when injected intramuscularly and better still when given slowly intravenously. Subcutaneous injection of drugs produces a well-sustained and fairly uniform action. The "depot" principle of therapy is seen in the use of subcutaneous "implants": sterile compressed pellets of a suitable preparation are deposited in the tissues by means of a trocar and cannula; the desired effects of the drug may thus be prolonged for several months.

*Intramuscular Injection.* The drug in solution or suspension is injected deeply into a large muscle. The best site is the upper and outer quadrant of the buttock. The rate of absorption is reasonably uniform and—if aqueous solutions are used—absorption is rapid. A sustained action of moderate intensity can be achieved by creating a "depot" of the drug in the muscle. For this purpose the drug is dispensed in oil or—more elegantly—it is modified chemically to retard the release of the active component into the blood stream. Mild irritants can be injected intramuscularly without causing intolerable pain.

*Intravenous Injection.* The solution is injected into the lumen of a vein and the characteristic effects of the drug are usually seen within half a minute. This rapidity of action is sometimes desirable, but intelligent anticipation of the patient's needs should make these occasions relatively rare, and the subcutaneous or intramuscular routes are commonly preferred. An intravenous injection should take at least one minute; and if the desired effect is achieved by giving a quarter or a half of the dose, the solution remaining in the syringe can be injected intramuscularly or withheld altogether. Intravenous therapy calls for technical skill to minimise the risks of leakage of irritant solutions into surrounding tissues. Local venous thrombosis is common following injections. The median basilic vein should not be used because of the hazard of injecting the drug into the nearby brachial artery.

*Intra-arterial Injection.* The injection is made into the lumen of an artery. Thus in a few seconds the drug is swept rapidly to its

site of action. Not only is it in high concentration in the arterial blood, but its potency is unattenuated by tissue enzymes. All these circumstances contribute to the production of grossly exaggerated pharmacological actions—always a source of anxiety for the physician and sometimes dangerous for the patient.

*Intraperitoneal Injection.* The peritoneum offers a very extensive surface from which drugs are readily absorbed. The obvious hazards of intraperitoneal injection, however, preclude its use if other methods are practicable. In infants and young children saline infusions are sometimes given intraperitoneally to combat the effects of dehydration.

*Injection into the Bone Marrow.* The needle is introduced into the marrow cavity. In adults the sternum is usually chosen but in young children the femur or tibia are preferred. The effects are similar to those following intravenous injection. The main indication for this route of administration is provided by the impossibility of giving the drug intravenously.

*Intrathecal Injection.* Injection is made into the subarachnoid space by lumbar puncture or into the cisterna magna. The effects of the drug are virtually restricted to the central nervous system. Intrathecal injection is often used to produce regional anaesthesia. Much less frequently this route is chosen for the administration of antibiotics in order to maintain a high concentration of the drug in proximity to the meninges and brain: thus streptomycin may be given intrathecally as one part of a scheme of treatment in tuberculous meningitis.

**INHALATION.** Oxygen and carbon dioxide, vapours of volatile liquids such as ether and cyclopropane and a variety of drugs prepared as aerosols are administered by inhalation. Absorption takes place through the pulmonary epithelium which presents a large absorbing surface: thus high blood levels can be attained rapidly.

**RECTAL ADMINISTRATION.** There are appropriate pharmaceutical preparations such as suppositories and aqueous solutions

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for topical medication of the rectum and sigmoid colon. They are mentioned elsewhere in this book. Occasionally drugs are given rectally for their systemic effects when oral administration presents difficulties—for example when the patient is nauseated or vomiting. Again, when it is desired to produce a relatively weak but sustained effect rectal administration warrants consideration. On the other hand, it is a somewhat inconvenient method of treatment and it is not widely used except in hospitals. In a different class are the evacuant enemas of warm tap-water which, by their bulk, excite peristalsis in the descending colon and cause immediate emptying of the bowel.

**EXTERNAL APPLICATION.** Most skin diseases call for the direct application of drugs externally, but in addition therapeutic effects are sometimes obtained from oral and parenteral therapy. There are many possible objectives in topical therapy: soft paraffin (Vaseline) to accelerate the healing of abrasions; water conveyed as a cold mucilage of starch (starch poultice) to soften skin crusts by maceration; salicylic acid in various ways as a keratolytic; numerous chemical compounds suitably dispensed to exert a localised antiseptic action, an antipruritic action, an irritant action in the process of counter-irritation, and many others. In general lotions are used when the skin lesions are moist or “weeping”; but when the lesions are “dry”, ointments or pastes are usually found more suitable. If lesions are small and not too numerous they can be touched with a camel-hair brush charged with a solution of the medicament.

**INSUFFLATION.** When the dry and finely powdered drug is blown into a body cavity or space and thus distributed on a tissue surface, the procedure is called insufflation. In general the method is apt to be cumbersome, and alternative methods of administration are usually preferred. There is no doubt, however, that many drugs given by insufflation are absorbed through normal tissues and granulating surfaces.

**SUBLINGUAL ADMINISTRATION.** A tablet containing the drug is placed under the tongue and allowed to dissolve in the

saliva; or it may be chewed and the particles retained in the mouth for a few minutes. Absorption is rapid and uniform. Nitroglycerin tablets may be taken in this way in angina pectoris (p. 311); and isoprenaline sulphate sublingually is often effective in aborting a commencing paroxysm of asthma.

#### THE FATE OF DRUGS AFTER ABSORPTION

Once it has been absorbed a drug may be dealt with in one of several ways. It may resist all the attempts of the organism to alter its chemical composition: it is then excreted unchanged—for example in the urine. More frequently it will be partly or completely metabolised. If the molecule is not completely disintegrated by metabolic processes but merely fragmented to form intermediate products, these can often be identified in the tissues or the excreta. The mechanisms which are available to the body for the breakdown, degradation or detoxification of drugs include oxidation, reduction and conjugation. When one or more of these processes are used the main route of excretion of the end-products is the urinary tract but other channels are the intestine (usually the mucosa of the colon), the bile ducts, the sweat glands, breast tissue (during lactation) and the lungs. For practical purposes, however, excretion in the urine and faeces is by far the most important. Conjugation means the process of natural synthesis whereby a drug or one of its breakdown products is joined to sulphuric, glucuronic or hippuric acids. It is thus rendered inactive and harmless to the organism, and the new substance is excreted in the urine. The rapidity with which the tissues destroy, modify and then eliminate the drug determines its duration of effect and the spacing of doses for the maintenance of satisfactory blood levels. If the organ or organs which detoxify or eliminate the drug are diseased, then prolonged effects may follow the use of therapeutic doses. Patients with hepatic or renal disease are thus likely to experience prolongation of the effects of drugs.

Storage of drugs within the body may also occur. Barbiturates are believed to be concentrated and stored in fatty tissues. The liver and bones may also act as storage organs for drugs. Storage mechanisms are of great importance to the physiologist and biochemist. When the material which is stored in the body depots

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is radio-active, new problems are created which are of special interest to the pharmacologist and the clinician.

### FACTORS MODIFYING THE RESPONSE TO DRUGS

**ROUTE OF ADMINISTRATION.** The route chosen is an important factor among those which determine the nature of the response to a drug. The more rapidly the drug reaches its site of action, the less likely is it to undergo dilution in the blood or attenuation by enzymes: its effects will therefore be rapid in onset, intense in character, and above all predictable. For example, acetylcholine is inactive when given by mouth as it is hydrolysed in the stomach and intestine. Even when large doses are given by intravenous injection it does not produce its characteristic effects because it is hydrolysed by the cholinesterases present in the blood. However, when it is given by intra-arterial injection the well-known nicotinic and muscarinic effects are readily produced by minute quantities. For experimental work in the lower animals it usually suffices to inject acetylcholine intravenously. In human therapeutics, however, acetylcholine is never used as such. When cholinergic effects are desired, relatively stable compounds are given either orally or subcutaneously; they are never given intravenously because they may cause cardiac arrest by simulating the effects of over-activity of the vagus.

**RATE OF EXCRETION.** If a drug is rapidly eliminated it may be difficult to maintain an effective blood level and frequent administration of high doses may be necessary. The use of depot preparations or of implants may help to overcome this difficulty, and it may occasionally be possible to delay excretion by other means. The use of probenecid with penicillin is an example. Probenecid appears to compete successfully with penicillin for receptors in the renal tubules. This delays the excretion of penicillin and high blood levels can thus be maintained.

### CUMULATION

If a drug is given at short intervals the body may be unable to dispose of it rapidly enough to prevent a rising concentration in the tissues. The main reason why this does not happen more



often is that the practitioner takes into account most of the circumstances which are briefly discussed in this chapter. Thus the amount given, the spacing of doses throughout the day and the administration of the drug in relation to meals are matters which are based on experience—the fruit of observation and experiment by previous generations. Thus a convention evolves regarding the most effective method of giving a particular drug in specified circumstances. Although, in general, the aim is to prevent “cumulation” of a drug in the body, there are times when controlled cumulation is therapeutically desirable. For example, when *digitalis* (foxglove) is used in the management of cardiac insufficiency, the dose schedule is such that the patient can excrete only a fraction of the active principles which are being absorbed. This process is in fact deliberately designed to cause “piling up” of the drug in the body, so that the therapeutic objective—to restore efficiency of the heart—can be achieved with a minimum of delay; and in the hands of an experienced clinician this can be done without the unpleasant side-effects of overdosage. At this point the dose must be rapidly reduced so that intake (daily dose) balances with output (excretion), thus ensuring that the beneficial effects of drug therapy are maintained and recurrence of cardiac failure is prevented: this is called the *maintenance dose* and it has to be determined by the clinician for the individual patient.

## DOSE

The appropriate dose of a drug is that which meets the needs of the individual patient at a particular time. It follows that only general guidance can be given on dosage. The British Pharmacopœia mentions a *range of doses* for official preparations—that is to say the minimum and the maximum dose: these are recommendations based on the usual requirements of an adult patient; they are not intended to apply in all circumstances. As a rule the intensity of the pharmacological action is proportional to the dose. The physician speaks of a *therapeutic dose*—meaning the dose which produces appreciable benefit to the patient: it usually falls within the pharmacological range of dosage. Excessive doses may cause some kind of distress and when such side-effects are

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conspicuous or serious in nature the dose may be called a *toxic dose*. Quantities considerably in excess of pharmacopœial "maximal" doses are sometimes necessary, but on these occasions the physician is alert to detect early toxic effects. The amount which kills the animal is called the fatal or *lethal dose*. In human beings, information about the lethal dose of a drug is of course acquired fortuitously: it comes from records of accidents and suicides. In lower animals however a deliberate attempt may be made to determine the lethal dose. A single observation would be almost valueless, and the design of a toxicity test aims at achieving a reasonably accurate approximation by exposing groups of animals to the poison under stated conditions.

The "LD 50" is the dose which kills 50 per cent of the population of animals to which it has been given. The "LD 95" kills 95 per cent. The term "ED 50" means the dose of drug which produces a given pharmacological effect in 50 per cent of the animals. The "ED 95" produces it in 95 per cent. The "MLD" is the *minimum lethal dose* as determined experimentally. The Therapeutic Index is the ratio

$$\frac{\text{LD}_{50} / \text{therapeutic dose}}{\text{or}} \\ \frac{\text{MLD} / \text{minimum effective dose.}}$$

For safety, the ratio should be appreciably greater than one. In other words, a drug is acceptable for therapeutic use only when its characteristic effects are produced by a dose much smaller than the toxic dose. Some latitude is essential if the doctor is to prescribe without undue anxiety on account of the varying susceptibility of individual patients.

The doses of drugs for *infants* must be learned in clinical practice and by reference to formularies (see BNF). In general *children* receive amounts that are proportional to their body weights, assuming that the weight of the average normal adult is 70 Kg. (say 150 lb.). There are also formulæ for calculating the dose

according to the age of the child. Thus  $\frac{\text{age}}{\text{age} + 12} \times \text{adult dose}$  means that a child of 6 years would receive one-third of the adult dose. Such formulæ are based on the assumption that the child's weight

is normal for his age; they do not relieve the doctor of the obligation to consider other factors influencing dosage. It must be noted also that there are reservations specifically applicable to children: they are tolerant of relatively large doses of *belladonna* and its alkaloids, but they are excessively sensitive to ordinary doses of morphine.

Medicines are taken after meals. This diminishes the risk of producing gastric irritation with its attendant nausea and vomiting. On the other hand, the admixture of the drug into the food lying in the stomach and upper intestine usually delays the onset of action—perhaps to the extent of an hour—and reduces its intensity. In ordinary circumstances such modifications are not serious disadvantages: on the contrary, they make for smooth induction of the desired effects. Nevertheless a drug may be given to the fasting patient with the deliberate intention of inducing its effect without undue delay: the action of a hypnotic can thus be enhanced, and the method is specially applicable to drugs prescribed for the prevention of travel sickness.

Sometimes a combination of two drugs causes a therapeutic effect which is greater than the expected sum of the individual effects: this phenomenon is known as *potentiation* or *synergism*. If the therapeutic effect equals the sum of the individual effects *addition* or *summation* has taken place.

In some cases the effects of a given dose of drug diminish as treatment goes on and larger and larger doses must be given to maintain the desired therapeutic effect. When this occurs the patient is exhibiting *tolerance* to the drug; it may also be said that he has become habituated, but the phrase is unfortunate because *habituation* must be distinguished from *drug-habit* and *addiction* (see below). In the laboratory the phenomenon of tolerance or habituation is demonstrable on animals and is described as *tachyphylaxis*.

Sometimes patients show unexpected effects following the administration of a drug in average or small doses, and not infrequently such effects are unpleasant and alarming: this is described as *idiosyncrasy*. Thus iodine or iodides may cause symptoms and signs resembling those of acute coryza, aspirin may cause urticaria and asthma, and barbiturates may produce a

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measles-like eruption. It should be noted that these untoward effects appear after the first dose; they are not related to overdose or cumulation but are the result of a sensitive state peculiar to the individual. Idiosyncrasy to certain foods is also well known—such as the occurrence of nettle rash after shell-fish.

The occurrence of allergic or anaphylactic reactions following the administration of a drug is described as *hypersensitivity*. This differs from idiosyncrasy: there is an initial sensitisation to the drug so that subsequent administration causes what appears to be an antigen—antibody reaction. The result may be a relatively mild disturbance such as urticaria or a severe reaction amounting to anaphylactic shock. Hypersensitivity reactions have been shown to occur to many drugs and they are seemingly unrelated to the inherent toxicity of the chemical or to its pharmacological properties. Hypersensitivity reactions occur even to penicillin, notwithstanding that its pharmacological actions are extremely limited and the fact that it is virtually non-toxic.

**ADDICTION.** Addiction may be described as “. . . a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated administration of a drug. Its characteristics are a compulsion to continue taking the drug and to increase the dose with the consequent development of psychic and sometimes physical dependence upon the drug's effects. Finally the development of means to continue the administration becomes an important or perhaps the only motive in the addict's life.”\*

**DEPENDENCE.** Not every person who claims to have become dependent on a drug should be regarded as an addict. The existence of a state of addiction is revealed by the nature of the *abstinence syndrome*. A patient's requests to continue medication with a hypnotic, for example, may indicate nothing more than the development of a conditioned reflex; and this situation is amenable to firm management by the physician. On the other hand, in the true addict the grave significance of the state of

\* Based on a definition of Addiction published by the *Expert Committee on Drugs Liable to Produce Addiction* of the WHO of the United Nations.

dependence is apparent in the severity of the abstinence symptoms: deprivation of the drug causes serious psychological upsets and—what is more significant—physical disturbances occur such as tachycardia, palpitation, salivation, sweating and diarrhoea.

#### CHEMICAL STRUCTURE AND PHARMACOLOGICAL ACTIVITY

The advances made in organic and physical chemistry during the present century are among the most notable in the history of science. These developments have had far-reaching effects on medical practice. Through the medium of experimental pharmacology new preparations have been tested and a large number of valuable drugs have been made available to the clinician. This work has not been done in random fashion: for the most part it has been the outcome of deductive reasoning. The pioneers in organic chemistry developed methods for ascertaining the molecular structure of chemical compounds. Such knowledge was used to explore the composition of many naturally occurring substances such as cocaine, atropine, quinine, morphine, tubocurarine and many others. Thus it became feasible to correlate pharmacological actions and molecular patterns; and even certain groupings within the molecule are now known to confer on a compound specific effects. The next step was to design and synthesise simpler molecules in the hope of obtaining predictable pharmacological actions uncomplicated by side-effects. This approach has proved its value on many occasions—notably in the creation of new local anæsthetics, using the molecular structure of cocaine as the starting point; and from the study of morphine many new analgesics have been evolved. It is established that certain chemical groups are associated with specific types of pharmacological activity. Most neuromuscular blocking agents are quaternary ammonium salts, and most of those which have been used clinically possess two quaternary nitrogen atoms situated at opposite ends of the molecule and about 12 to 14 Ångström units apart. This relationship can be seen in tubocurarine; and when it was postulated that this might be significant in relation to the specific action of the drug, many simpler compounds were made on the same pattern. Decame-

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thonium, suxamethonium, laudexium and benzoquinonium all possess two quaternary nitrogen atoms separated by chains about 14 Ångström units long. Although many assumptions have been made about the necessity for the type of structure described, it must be remembered that  $\beta$ -erythroidine is a tertiary base and C-curarine and C-toxiferine are monoquaternary indolic bases. These three compounds are potent muscle relaxants. It is tempting to speculate upon the development of research on synthetic neuromuscular blocking agents if one of these had been as readily available as tubocurarine.

The ganglion-blocking agents again appear to show that there is a critical relationship between structure and activity. Hexamethonium, pentolinium and others are bisquaternary salts. The quaternary nitrogen atoms are separated by a chain which is shorter than that separating them in the neuromuscular blocking agents. It has been shown recently that mecamlamine which is a secondary base can effectively cause ganglion-block, and nicotine which is a tertiary base causes an intense long-lasting blockade.

Atropine-like anticholinergic activity seems to be associated with a slightly more complex chemical structure. The configuration necessary appears to be made up of a chain: at one end there is a quaternary carbon atom carrying a heavy aromatic substituent and this is separated by a short carbon or carbon-oxygen chain from a tertiary nitrogen atom. No set rule has yet been identified, but a number of compounds which incorporate in their molecules the structure described have potent atropine-like activity. There is a great deal still to be learnt about the relationship between structure and function. It would be difficult to exaggerate the value of positive findings such as those mentioned above. On the other hand it is clear that a particular effect on the living organism can often be attained by using substances which differ widely in their chemical composition. For example, many of the hypnotic drugs are totally dissimilar in their chemical composition and molecular structure. Again, it must be recorded that a great deal of work directed to improving the action of existing preparations has been unrewarded by any advances of immediate practical importance. Atropine, tubocurarine and

digitalis have not been improved upon, notwithstanding the synthesis of hundreds of alternative compounds.

In particular, until much more is known of cellular metabolism, attempts to predict pharmacological activity solely from our concepts of molecular structure must meet with only limited success. Laboratory studies must be carried out and even then wide quantitative and qualitative variations in activity will probably be found to exist between various species and between individuals in the same species. The ultimate and most important step is the assessment of pharmacological activity in the higher animals and especially in man, because this knowledge is indispensable to clinicians who undertake medical and veterinary practice.

## CHAPTER 2

# PHARMACOLOGY OF RENAL FUNCTION

THE essential function of the kidney is to maintain constancy of the volume and composition of the body fluids. It eliminates or conserves water and electrolytes according to circumstances. With the lungs it plays an important role in maintaining the acid-base equilibrium and in getting rid of metabolic end-products. It is also the chief channel of elimination for most drugs, and when renal function is impaired signs of cumulation may readily appear. Many drugs in passing through the kidney leave its functions untouched; others temporarily modify its activity causing an increase in urine flow (*diuretics*) or a decrease in urine volume (*antidiuretics*). Some of the former block selectively certain tubular functions to cause diuresis. Some drugs are excreted by the tubule, e.g., penicillin, and there are others which can prevent such excretion by occupying the common transporting enzyme system (*tubular blocking agents*). A few drugs have a *nephrotoxic effect*, i.e. they are capable of damaging the cells of the kidney.

### DIURETICS

Diuresis can be produced in a variety of ways ranging from the drinking of water to the parenteral injection of a mercury compound. An account will now be given of how the physiological processes concerned with urine formation can be modified by drugs.

### THE SECRETION OF URINE

*The secretion of urine* is a complex affair involving two major processes: (1) the filtration of tissue fluids by the glomerulus, and (2) the modification of this fluid by tubular activity. The force causing glomerular filtration is the blood pressure in the glomeru-



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lar capillaries and this is opposed by the osmotic pressure of the plasma proteins. About 20 per cent of the plasma fluid passes into the proximal end of the tubules. The volume of filtrate amounts to about 180 litres per 24 hours. Tubular reabsorption reduces this large volume by 99 per cent to give a volume of 1-2 litres of hypertonic urine.

The volume of urine can be increased theoretically either by increasing the volume of glomerular filtrate or by diminishing the amount of fluid reabsorbed by the tubule. The latter is the much more efficient method as Table I illustrates.

TABLE I

To show the relative efficiencies of (a) increasing glomerular filtration and (b) reducing tubular reabsorption, in promoting diuresis.

	Filtered by glomeruli	Reabsorbed by tubules	Urine volume
Normal . . . . .	180.0 litres 24 hrs.	178.2 litres 24 hrs. (99%)	1.8 litres 24 hrs.
Glomerular filtration increased by 10% . . . . .	198.0 litres 24 hrs.	196.02 litres 24 hrs. (99%)	1.98 litres 24 hrs.
Tubular reabsorption decreased by 1% . . . . .	180.0 litres 24 hrs.	176.4 litres 24 hrs. (98%)	3.6 litres 24 hrs.

A drug may be given which will increase glomerular filtration by 10 per cent and if tubular activity remains unaltered, the increase in urine volume would be 10 per cent. If, on the other hand, tubular reabsorption were diminished by as little as one per cent, the urine volume would be doubled. *The most efficient diuretics are thus those which act by diminishing tubular reabsorption.* It is relevant to note here, however, that in congestive cardiac failure, the most common clinical condition for which diuretics are prescribed, there is poor glomerular filtration caused by poor renal blood flow. Rational therapy is primarily directed to restoring cardiac efficiency and thereby renal blood flow and glomerular filtration. The powerful diuretic effect of digitalis in these circum-

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stances is thus an indirect one (digitalis, p. 291; discussion on use of diuretics in cardiac failure, p. 49). Of the commonly used diuretics which act directly on the kidney (primary diuretics), all diminish tubular reabsorption. One group of primary diuretics, the xanthines, also increases glomerular filtration.

**TUBULAR FUNCTIONS.** The cells lining the renal tubules contain enzyme systems which selectively extract certain constituents of the glomerular filtrate for return to the blood. Other enzyme systems actively secrete into the tubular urine certain ions and drugs. In addition the tubular cells allow passive diffusion between tubular urine and blood of such substances as urea, alcohol and the volatile anæsthetics.

1. *Selective Reabsorption.* As the glomerular filtrate passes through the proximal tubule its volume is substantially reduced; 80 per cent passes back to the blood in an isotonic state. This reabsorption is not indiscriminate but highly selective, involving a return to the blood stream of essential plasma constituents such as salts, glucose and water; and the rejection of excess salts taken in the food, waste products such as creatinine, and foreign substances such as inulin and many drugs. The process of reabsorption is controlled by enzyme systems which actively transport the anions of salts. With each anion, a cation will be reabsorbed and with each molecule of salt an isosmotic amount of water will move towards the blood stream. Thus each mille-equivalent of  $\text{Cl}^-$  absorbed will be accompanied by one mille-equivalent of base (mainly  $\text{Na}^+$ ) and under osmotic pull approximately 7 ml. of water will diffuse with the salt. There is evidence that the enzyme system promoting chloride reabsorption is specifically inhibited by mercury compounds. Likewise carbonic anhydrase concerned with the reabsorption of bicarbonate is inhibited by acetazolamide. Glucose also is reabsorbed by an enzyme mechanism which can be inhibited by phloridzin. There is thus a group of drugs which act as diuretics by temporarily depressing the enzyme systems concerned with isosmotic reabsorption in the first part of the tubule. These enzyme systems can also be overloaded by giving salts or glucose in such quantity that they appear in the

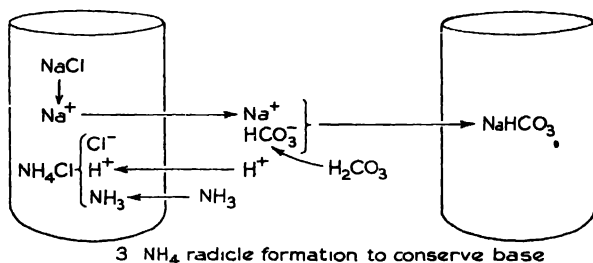
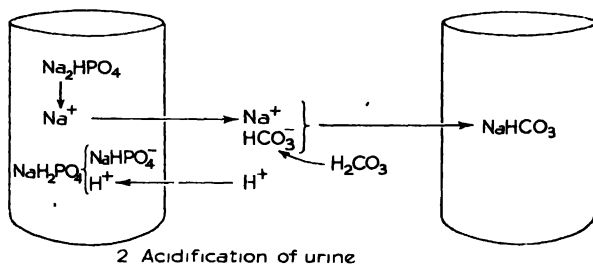
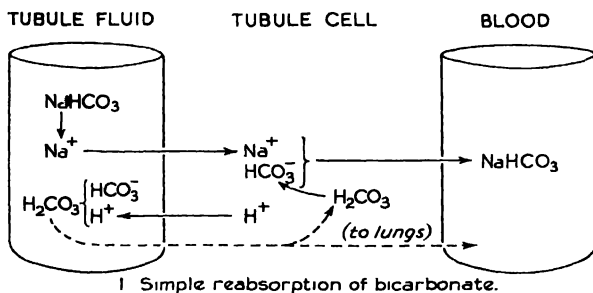
glomerular filtrate in concentrations which are beyond the reabsorptive capacity of the tubules. The unabsorbed fraction will retain an isosmotic amount of water within the tubule and so cause diuresis. This is sometimes referred to as osmotic diuresis. There is a further group of salts and sugars which also cause an osmotic diuresis. These are the non-threshold substances—sulphates, nitrates, sucrose and mannitol. These readily appear in the glomerular filtrate; the nitrates and sulphates are sparingly reabsorbed; and sucrose and mannitol are untouched by the tubule as it lacks mechanisms for their reabsorption. Urea is also an osmotic diuretic. As the glomerular filtrate passes down the tubule, urea diffuses through the tubular walls back to the blood and normally about 50 per cent is in this way reabsorbed. When high concentrations of urea are present in the filtrate such as occur after administration of 15–25 G., the rate of passage down the tubule will not permit equilibration by diffusion of urea between tubular urine and blood. The unabsorbed urea by virtue of its osmotic pressure retains water in the tubule and so augments urine volume.

2. *The specific reabsorption of water* occurs in the distal part of the renal tubule and is promoted by the antidiuretic hormone (ADH) of the neurohypophysis. Water only is reabsorbed and the urine is concentrated. The specific reabsorption of water diminishes when there is less antidiuretic hormone available; water and alcohol owe their diuretic action to this mechanism.

3. *Tubular Secretion.* The cells of the tubules actively secrete into the tubular urine hydrogen and potassium ions. The reabsorption of bicarbonate by the tubules involves an exchange of  $H^+$  in the cell with  $Na^+$  in the glomerular filtrate. In this sense  $H^+$  is secreted by the tubules. The source of  $H^+$  is carbonic acid, the formation of which from carbon dioxide and water is catalysed by carbonic anhydrase. The three reactions in which  $H^+$  is exchanged for  $Na^+$  are illustrated in the following diagram.

These reactions lead to 1. the simple reabsorption of bicarbonate; 2. the acidification of the urine by increased formation of  $NaH_2PO_4$ ; and 3. in acidosis and in sodium depletion, the for-

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mation and excretion of  $\text{NH}_4^+$  radicle. In each case  $\text{Na}^+$  is returned as the labile bicarbonate to augment the alkali reserve of the blood. When the availability of the  $\text{H}^+$  is limited by inhibition of carbonic anhydrase by acetazolamide such reabsorption of sodium does not occur. This leads to an acidosis in the blood and to the loss in the urine of large quantities of bicarbonate, sodium, potassium and water.

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It is now thought likely that potassium found in the urine is actively secreted by the tubules. The mechanism is not clear but the available evidence points to a reciprocal relationship between  $H^+$  and  $K^+$  with regard to  $Na^+$  exchange. Thus when alkalosis exists a diminished secretion of  $H^+$  permits an alkaline urine to be formed and an increased quantity of  $K^+$  is found in the urine. Following the ingestion of large quantities of  $K^+$  the increased excretion of  $K^+$  is accompanied by an alkaline urine from the suppression of  $H^+$  secretion; and when  $H^+$  secretion is inhibited by acetazolamide increased quantities of  $K^+$  are to be expected in the urine.

The diuretics will be described in the following order:

### 1. PRIMARY DIURETICS which act directly on renal function.

- (a) *Inhibitors of ADH secretion*—water, alcohol.
- (b) *Inhibitors of enzyme systems* concerned with isosmotic reabsorption—organic mercurials, acetazolamide, chlorothiazide, amismetradine, xanthines.
- (c) *Osmotic diuretics*—certain salts and sugars, and urea.
- (d) *Acid diuretics*—ammonium chloride, calcium chloride.

### 2. SECONDARY DIURETICS which permit renal water loss by an extra-renal action.

- (a) *Cation exchange resins* which cause sodium loss in the faeces.
- (b) *Agents which increase the osmotic pressure of the plasma proteins*—albumin, dextran, acacia.
- (c) *Digitalis* which promotes diuresis in cardiac failure by an action on the heart.

**INHIBITORS OF ADH SECRETION.** *Water* is the natural diuretic. When taken in quantity it lowers the osmotic pressure of the plasma electrolytes and thereby inhibits the secretion of the anti-diuretic hormone (ADH) from the pituitary. Lacking ADH the distal tubule is unable to reabsorb water and within 30 minutes of drinking water an increased flow of dilute urine occurs lasting for 1–3 hours depending on the quantity consumed. As the blood is cleared of the water load the osmotic pressure of the electro-

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lytes rises, ADH is again secreted and a concentrated urine of low volume appears. The presence of normal quantities of hydrocortisone is necessary for such a diuresis. In adrenal insufficiency a prompt diuretic response to water is not obtained.

*Uses.* Water is of no value in promoting diuresis in œdema where an excess of water is retained, commonly from a primary retention of sodium. It has however important uses in maintaining the solubility of drugs in the urine and in promoting the excretion of waste products in fevers.

*Alcohol* has a similar action to water in inhibiting secretion of ADH but is not used as a diuretic.

INHIBITORS OF ENZYMATIC REABSORPTION. *Organic Mercurials.* When *inorganic* forms of mercury such as calomel or grey powder are taken by mouth a mild and variable degree of diuresis results from the renal action of the absorbed mercury ion. Most of the mercury remains in the bowel and therefore produces purgation, but a small and unpredictable amount enters the blood stream and is slowly eliminated, chiefly by the kidneys. Inorganic mercurials are thus not dependable diuretics; and they have the serious disadvantages of producing purgation and, with repeated use, of causing chronic mercury poisoning. In contrast certain *organic* mercurial compounds are reliable diuretics and the most powerful available. These preparations have to be injected intramuscularly—and this is a disadvantage compared with oral administration. Properly used, however, they are safe—because the metal is bound in the form of a complex molecule and ionisation is slow; and a dose of a mercurial diuretic is almost entirely excreted before the next is given. Similar preparations are available for oral administration (see below) but on the whole they are not dependable. Other organic mercurial compounds are local antiseptics. The mercurial diuretics are complex organic acids containing  $\text{Hg}^+$  in the anionic radicle and are prepared as sodium salts for administration. The official mercurial diuretic is *Mersalyl* which contains 40 per cent mercury. The preparation used is Mersalyl Injection BP—a 10 per cent solution containing also 5 per cent theophylline. The dose of the Injection is 0.5–2.0 ml. Mersalyl is irritant to the tissues and is commonly given deeply

intramuscularly. Theophylline is included for pharmaceutical reasons: it enhances the stability of the mersalyl solution. Although theophylline, with other xanthines, has a diuretic action, the quantity contained in Mersalyl Injection is too small to contribute significantly to the diuretic action of the preparation.

*Excretion of Mersalyl.* When given intramuscularly mersalyl is readily absorbed and it is quickly excreted by the kidneys. Fifty per cent of the dose is eliminated in 3 hours, and by the end of 24 hours more than 90 per cent.

*Diuretic effect.* Diuresis begins in 2 to 3 hours, is maximal in about 8 hours and passes off in 12-24 hours. The dose should therefore be given early in the day—say at 6 a.m.—to ensure that the diuretic effect is largely over by the evening; thus sleep is not disturbed unduly. In water-logged cardiac patients the effect is frequently dramatic: 3 to 10 litres of urine may be excreted. As the œdema is cleared the diuretic response to mersalyl becomes less.

*Mode of action.* During excretion by the kidney some molecules of mersalyl become temporarily attached to the cells of the tubules. The  $\text{Hg}^+$  in the molecules unite with the -SH groups of the enzyme concerned with chloride reabsorption, thereby paralysing the system. Large quantities of chloride with associated sodium and potassium are thus not reabsorbed and are excreted with an isosmotic amount of water. A temporary fall in the chloride level of the plasma occurs but this is soon restored by salt taken in the food and by the compensatory action of the kidney.

*Administration.* The initial dose of Mersalyl Injection is small—0.5 ml. intramuscularly. This is simply a precaution aimed at detecting the patient who has an idiosyncrasy to mercury and who might become acutely ill if he received a full dose of mersalyl. Patients sensitive to mercury may develop excessive salivation, diarrhœa, albuminuria or hæmaturia. Shivering, fever, headache, nausea, vomiting and a red blotchy rash are allergic manifestations. These untoward effects are rare; when they occur, further

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doses of mersalyl should not be given. When the reaction is *allergic* in type, a test dose of another mercurial diuretic should be tried.

If no untoward effect appears following the test dose, intramuscular injections of 1-2 ml. are given every 2, 3 or 7 days as the œdematous state requires. If injections are given daily there is some risk of cumulation and mersalyl unresponsiveness may be quickly induced. (*See below—Secondary Toxic Effects.*)

Mersalyl Injection may also be given intravenously. By this route the discomfort of the intramuscular route is avoided and the diuresis has an earlier onset, is more intense and of shorter duration. The risk to the patient however is much greater. There are a few people who are extremely sensitive to mercury and in these the introduction into the blood stream of a mercurial diuretic may cause sudden death from ventricular fibrillation. Should intravenous administration be considered necessary, the dose of the official injection should not be more than 1 ml. This should be diluted with 10 ml. of saline solution and injected very slowly. Leakage of mersalyl outside the vein causes an inflammatory reaction with brawny œdema, and sloughing may occur.

*Unofficial Mercurial Diuretics.* There are no important differences between mersalyl and the unofficial organic mercurials. They are valuable alternative preparations for patients who are allergic to mersalyl. *Meralluride* (USP) ("Mercardan") is alleged to be less irritant locally. *Mercuramide* ("Neptal") is prepared in 1.8 per cent solution for intravenous injection as well as a 9 per cent solution for intramuscular use. *Mercaptomerin* ("Thiomerein") contains no theophylline which is replaced in the molecule by a mercaptide group. This compound is less irritant locally than the others and has been recommended for subcutaneous use. Local reactions, however, occur in 20 per cent of patients. Other disadvantages include the need to prepare the solution for injection from the dry powder, and a tendency to induce allergy. *Tablets* of mercurial diuretics are available for oral use. In general they are unsatisfactory as the tolerance of the bowel for mercury is low and purgation is a common side-effect. Some patients with recurring slight œdema find that a weekly dose of tablets can replace injections.



Tablets of chlormerodrin ("Mercloran") and of mercuramide ("Neptal") are available. Suppositories containing mercurial compounds have proved to be unsatisfactory: irritation of the rectum often causes purgation, and absorption into the blood stream is variable.

*Toxic Effects of the Mercurial Diuretics.* Considering the frequency with which mersalyl is used the incidence of toxic effects is low. Sudden death immediately following *intravenous* injection is the major hazard and results from a direct toxic effect of the mercurial on the myocardium. This is now very rare because mercurials are seldom given by the intravenous route. Less serious effects may occur shortly after intramuscular injection and these have already been described (p. 32). Skin rashes of various kinds may be seen during treatment with mersalyl. The commonest form is an erythema, but urticarial and petechial types occur. Very occasionally a dermatitis is produced which may proceed to the grave condition of exfoliation. Signs of chronic mercury poisoning—proteinuria, hæmaturia, diarrhœa and hypersalivation—occur when impaired renal function is responsible for a slow rate of excretion of the drug. Likewise too frequent administration or hypersensitivity may be responsible for signs of mercurialism. Any *severe* untoward reaction to mersalyl should be treated by prompt injection of dimercaprol (see p. 590).

*Secondary Toxic Effects.* Since mercury promotes the renal excretion of electrolytes and water, excessive losses of chloride, sodium, potassium and water may be seen as secondary toxic effects. These states of depletion commonly arise when the salt and water intake is limited—often by design but sometimes because of the anorexia which is characteristic of severe illness. *Chloride depletion* is the most common. It is to be suspected in a patient who after responding initially to mersalyl fails to have a diuresis from subsequent injections while still œdematous. Confirmation of the depletion can be obtained by finding in the plasma low chloride and high bicarbonate levels. The sodium level is usually little disturbed. Such a hypochloræmic alkalosis can be corrected by giving ammonium chloride 2 G. 4-hourly for 2 days

before the next mercurial injection. By raising the plasma chloride and thus the chloride load in the tubules, the diuretic effect of mercury will be restored. *Sodium depletion* may accompany chloride depletion and cause malaise, weakness, drowsiness and muscle pains. Mental confusion and hypotension may also be seen. A rising blood urea and a low sodium level in the plasma give objective confirmation. Relief is quickly obtained by giving sodium chloride. *Potassium depletion*. Excessive loss of potassium rarely occurs when mersalyl alone is being used. But if it is given after severe sodium restriction and prolonged medication with ammonium chloride, excretion of potassium will be promoted. It may not be possible to demonstrate a low plasma potassium level, but depletion is revealed clinically in the digitalis-maintained patient by the appearance of signs and symptoms of digitalis poisoning, one or two days after a copious mercurial diuresis. Digitalis intoxication (p. 292) occurring after diuresis was formerly attributed to mobilisation of digitalis glycosides in the œdema fluid. It is now established that potassium loss from the body sensitises the heart to the action of digitalis. When digitalis poisoning occurs in these circumstances, digitalis should be stopped and potassium chloride given until the signs of overdosage have disappeared.

*Uses.* The main use of organic mercurial compounds is to promote diuresis in the *œdema of cardiac failure*. No other type of diuretic approaches mercury in efficiency. In the patient with generalised dropsy Mersalyl Injection should be given from the start of treatment along with digitalis and sodium restriction. In the mild and moderate cases of congestive failure digitalis alone may be sufficient, but mersalyl will be required if œdema persists when the patient is fully digitalised. A poor response to mersalyl in a patient with cardiac œdema indicates the need for ammonium chloride. When mersalyl and ammonium chloride fail to be diuretic in the fully digitalised œdematous patient a copious diuresis can often be induced by giving aminophylline (p. 665) intravenously 3 hours after the dose of mersalyl. At this time the mercurial is acting fully on the tubular cells; and aminophylline—by causing an increase in glomerular filtration—

delivers to the tubules a large chloride load which cannot be reabsorbed and is therefore excreted. An important use of mersalyl is in the prevention of cardiac asthma—paroxysms of breathlessness at night which may occur in *left ventricular failure*. In this condition œdema fluid, though it is not perceptible on clinical examination, collects in the tissues during the day and during the night re-enters the vascular compartment and thus increases the load on the heart. If the left ventricle is failing, the heart cannot take the extra load: the pulmonary vessels become congested giving rise to acute dyspnœa. Mersalyl, by removing the œdema fluid via the kidney prevents the nocturnal paroxysms of dyspnœa. The use of mersalyl in *kidney disease* is very limited. The œdema of the nephrotic syndrome can sometimes be relieved temporarily and without damage to the kidney by the cautious use of mersalyl; but in all other renal diseases mersalyl is contra-indicated since its clearance will be retarded and there is a risk of causing further damage to kidney tissue. In the *ascites* of *hepatic cirrhosis* mersalyl and salt restriction can often replace intermittent paracentesis of the abdomen.

The need to administer mercurial diuretics by injection constitutes the major disadvantage of this class of compound. The search for diuretics which are effective when given by mouth led to the introduction of acetazolamide, aminometradine, amismetradine and chlorothiazide.

**ACETAZOLAMIDE.** Two sulphonamide compounds, sulphanilamide and acetazolamide, have diuretic properties by virtue of their ability to prevent reabsorption of bicarbonate in the tubular urine. Both act by inhibiting carbonic anhydrase but acetazolamide is much more powerful and is less toxic than sulphanilamide. Acetazolamide ("Diamox"), a heterocyclic sulphonamide, was specially prepared as an inhibitor of carbonic anhydrase. It has no bacteriostatic action. Given orally it is rapidly absorbed and most of it is excreted by the kidneys in 12 hours. It undergoes little change while in the body.

*Mode of Action.* Acetazolamide has only one pharmacological action; it is a powerful inhibitor of carbonic anhydrase. This

enzyme is present in many tissues—kidneys, gastric mucosa, pancreas, brain and red cells. Its function is to catalyse the formation of carbonic acid from carbon dioxide and water, the equation being  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H.HCO}_3$ . Thus the enzyme normally makes readily available a supply of  $\text{H}^+$  and  $\text{HCO}_3^-$  ions. In the kidney, this availability of  $\text{H}^+$  in the tubular cell makes possible the exchange of  $\text{H}^+$  for  $\text{Na}^+$  in the tubular urine and leads to the reabsorption of bicarbonate and to the acidification of the urine (p. 29).

When acetazolamide is given, carbonic acid is not formed in adequate amounts to provide sufficient  $\text{H}^+$  for the complete reabsorption of  $\text{HCO}_3^-$ . The unabsorbed bicarbonate with associated base and an isosmotic quantity of water are thus retained within the tubular lumen and excreted. The urine is alkaline in reaction on account of the high bicarbonate content and increased quantity of disodium hydrogen phosphate. Large quantities of sodium and potassium are also excreted (p. 29). Since chloride reabsorption is not affected, the chloride plasma level remains normal or is increased; the bicarbonate level is reduced by loss in the urine. An acidosis thus exists. The diuretic effect of a single oral dose lasts for 6–12 hours. By this time most of the drug is excreted and the kidney once more reabsorbs bicarbonate; acid-base equilibrium is restored 24 hours after taking the dose of acetazolamide. Restoration of the plasma bicarbonate level is necessary for diuresis from subsequent doses of the drug. Hence for diuretic purposes a dose is given daily or once every 2 days. Continuous administration of acetazolamide i.e. 6- or 8-hourly, will not cause persistent diuresis. Only an initial increase in urine volume occurs. When the blood bicarbonate is lowered the bicarbonate delivered to the tubules is necessarily also diminished and acetazolamide cannot act as a diuretic; however, a chronic acidosis is produced. For certain non-diuretic uses of the drug, continuous therapy is necessary.

The carbonic anhydrase in the renal cells seems to be more susceptible to inhibition by acetazolamide than that in other tissues. The transport of  $\text{CO}_2$  by the red cells which is dependent on carbonic anhydrase activity is little disturbed by very large doses of the drug. Inhibition of the acid secretion of the stomach

and of bicarbonate secretion of the pancreas can be demonstrated in animals but only after large doses. These actions have no practical application in therapeutics. However, in the eye where the availability of bicarbonate seems to be necessary for the formation of the aqueous humour, acetazolamide is able to diminish its secretion. This action of the drug is used in glaucoma where the intra-ocular tension of the eye is increased through faulty drainage. In the nervous system acetazolamide has an anti-convulsant action which is probably due to inhibition of carbonic anhydrase in the brain. The precise mode of action is not yet known and the possibility exists that the acidosis induced by renal loss of bicarbonate plays at least some part in the diminished susceptibility to convulsions.

*Administration.* Tablets containing 250 mg. are available for oral use. For intravenous use the sodium salt is prepared as a dry powder to be dissolved in water before injection. The dose to be given varies with the condition being treated.

*Toxic effects* seem to be rare. They are of three types: 1. drowsiness and paræsthesiæ of the face and extremities seen occasionally after large doses of the drug or on continuous administration; 2. sensitivity reactions similar to those seen with other sulphonamide drugs; and 3. secondary toxic effects from excessive loss of sodium and potassium.

*Uses.* In cardiac œdema it is less effective than the mercurials but it does not require injection and may be less toxic. Given as a single dose of 250 or 500 mg. daily to mild and moderate cases of congestive failure it will promote diuresis. As the œdema lessens the interval between the doses should be lengthened. Some patients with only slight cardiac insufficiency can be maintained free of œdema by giving two or three doses weekly. For severe cardiac œdema a mercurial is much to be preferred since its action is more certain. Acetazolamide fails at times to produce diuresis in such cases and often causes marked distortion of the electrolyte patterns in the plasma. When unresponsiveness to mercurials is due to hypochloræmic alkalosis, acetazolamide can

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be given to promote excretion of bicarbonate and thus restore the diuretic response of mercury; but a more reliable way of restoring the plasma chloride level is to give ammonium chloride. Acetazolamide is now being tried as an anticonvulsant in epilepsy and gives promise of being a useful adjunct to the standard treatment of the refractory case. Its use to limit the production of aqueous humour in glaucoma is rational and it offers a new approach to the treatment of this condition. Conventional methods of treatment of glaucoma are all directed to the promotion of increased drainage from the anterior chamber. In both these conditions, in contrast to the intermittent dosage for diuretic purposes, continuous administration with 6- or 8-hourly doses is required. Chronic acidosis is an inevitable side-effect.

CHLOROTHIAZIDE ("Saluric") is a new potent diuretic agent which is administered orally. Chemically it may be regarded as a substituted sulphonamide. It was synthesised as a possible carbonic anhydrase inhibitor but in man this action is minimal. It promotes the excretion of chloride and sodium and thus resembles mercury in its renal action. It causes only a minor increase in the excretion of potassium and bicarbonate. Unlike mercury its diuretic action is not inhibited by the existence of a hypochloræmic alkalosis; and it differs from acetazolamide in being effective in acidosis. The mode of action of chlorothiazide is not known, but it seems probable that it interferes with enzyme systems concerned with the tubular reabsorption of chloride and/or sodium. In addition to its diuretic action, chlorothiazide has a hypotensive effect. This is not seen when the blood pressure is normal but in hypertension reduced levels are obtained by use of this drug. The hypotensive effect is particularly marked in those already having reserpine or ganglionic blocking agents. Whether this action is solely due to the loss of sodium from the body is not yet known. The place of chlorothiazide in the treatment of hypertension remains to be defined.

Given orally chlorothiazide is readily absorbed and begins its diuretic action within 2 hours. The maximum effect is reported to occur between 4 and 8 hours, but the diuresis may continue for as long as 24 hours. Tolerance does not readily occur. Half the

dose of chlorothiazide is excreted in 24 hours; almost all is eliminated within 48 hours.

*Side-effects* are uncommon. It is now established however that they do occur. As might be expected they resemble those produced by other sulphonamides: nausea, anorexia, skin rashes and generalised sensitivity reactions may be seen; thrombocytopenic purpura has also been recorded and attributed to depression of the bone marrow. The use of chlorothiazide has also occasionally resulted in potassium depletion, particularly in those patients whose food intake (and therefore potassium intake) is poor. In such circumstances the administration of potassium chloride in doses of 2-6 G. daily is recommended (enteric-coated capsules are used).

*Uses and Dosage.* Chlorothiazide can be used in the treatment of congestive cardiac failure with œdema. In mercury-refractory cases of œdema, the simultaneous administration of mersalyl and chlorothiazide may induce an adequate diuresis.

In œdema of renal origin chlorothiazide appears to be effective and safe. In the ascites of liver cirrhosis it is also diuretic, but when hepatic function is poor coma may be induced by further loss of potassium. In pre-eclampsia diuretic and hypotensive actions have been demonstrated.

The drug is available as 0.5 G. tablets; the usual dose is 1-2 G. orally in the morning.

AMINOMETRADINE ("Mictine"), an amino-uracil derivative, is an oral diuretic which is less potent than mersalyl. It may be used for the ambulant cardiac patient to prevent accumulation of œdema fluid. The dose is 0.2-0.8 G. on alternate days. Side-effects are common and include loss of appetite, nausea, vomiting, headache, tinnitus and albuminuria.

AMISOMETRADINE ("Rolicton") is much less toxic than aminometradine especially with regard to vomiting. Larger doses may thus be given, e.g. 0.4 G. thrice daily. Such dosage given for 2 days has 40 per cent of the diuretic activity of 2 ml. of Mersalyl Injection.

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**THE XANTHINES.** The diuretic effect of drinking tea or coffee is not solely due to the volume of fluid consumed. These beverages contain methylxanthines which have diuretic properties as well as important actions on other tissues (p. 175). Caffeine, a trimethylxanthine, found in tea and coffee, is not used as a diuretic for it has a relatively weak action on the kidney and has a marked stimulant effect on the brain. Theobromine, a dimethylxanthine from cocoa beans has no central stimulant action and has a mild sustained diuretic effect. Another dimethylxanthine found in tea but largely made synthetically is theophylline which is the most powerful diuretic of this group.

*Action on the Kidney.* The xanthine diuretics have a two-fold action on the kidney. They diminish tubular reabsorption of the glomerular filtrate and thus promote diuresis. Their mode of action in interfering with tubular function is not known. This effect on the tubules can be demonstrated in oedematous cardiac patients given theophylline or theobromine orally; but the diuretic response is mild. A further renal effect appears when a large dose of a xanthine is injected parenterally. If 0.25 G. aminophylline (theophylline with ethylenediamine) is given intravenously there is a marked increase in renal blood flow and glomerular filtration rate. This action is achieved by the high blood levels of theophylline which stimulate the myocardium directly and open up the renal vessels by a direct action on their musculature. This renal vascular response is evanescent in healthy subjects but in patients with cardiac failure it may last for 30 minutes.

*Preparations.* Since the dimethylxanthines are insoluble alkaloidal bases they are prepared for use as soluble double salts, theobromine and sodium salicylate (dose 0.6–1.2 G.), and theophylline and sodium acetate (dose 0.12–0.3 G.). Aminophylline is another form of theophylline in which solubility is achieved by union with ethylenediamine (dose 0.1–0.5 G.). These compounds are available as tablets which are taken after food since gastric irritation is liable to occur, particularly with theophylline. The most effective is aminophylline since it is better absorbed than



the others but full therapeutic doses may not be tolerated by the stomach. To offset this disadvantage, aluminium hydroxide may be given along with each dose of aminophylline. Several new theophylline compounds which are alleged to be less irritant are at present under clinical trial. Theophylline sodium glycinate, dihydroxypropyltheophylline and theophylline ethanoate of piperazine, while less irritant are not so well absorbed as aminophylline. Choline theophyllinate is as effective as aminophylline but is probably as liable to cause epigastric discomfort.

*Uses.* As diuretics the xanthines are weak compared with mercury, and are employed only occasionally to prevent the recurrence of œdema in cardiac patients. An important use of aminophylline is to increase glomerular filtration when this is still poor in the œdematous cardiac patient who is fully digitalised. In these circumstances mercury is ineffective as a diuretic, since the volume of filtrate delivered by the glomerulus is so small that the tubule readily reabsorbs it. The combined use of mersalyl and aminophylline frequently causes a brisk diuresis. An intravenous dose of 0.25 G. aminophylline given 3 hours after the dose of mersalyl often produces a marked increase in glomerular filtration at a time when chloride reabsorption is strongly inhibited by the mercury. The injection of aminophylline should be given *slowly* intravenously. If given rapidly into a vein, flushing, hyperpnœa, dizziness and faintness may result, and sudden death has been reported. By the intramuscular route aminophylline causes severe local pain; but this can be avoided by the addition of 0.2 ml. of 2 per cent procaine hydrochloride solution to the syringe loaded with aminophylline.

**OSMOTIC DIURETICS.** The osmotic diuretics consist of the soluble salts of sodium and potassium; urea; and the sugars, sucrose and mannitol. When in the blood they readily appear in the glomerular filtrate. Since they are not reabsorbed or are present in quantities beyond the tubular capacity for reabsorption, they restrain the reabsorption of water by virtue of the osmotic effects which they exert in the tubular lumen. As a class they are not very potent diuretics.

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POTASSIUM SALTS are the most effective of the saline diuretics. When given in quantity the  $K^+$  is secreted by the tubular cells,  $H^+$  secretion being thereby diminished (p. 29). As a result bicarbonate is not reabsorbed and an alkaline urine is produced containing increased quantities of sodium and potassium. Good renal function is an essential requirement for the administration of potassium salts. Failure to excrete potassium will readily cause the features of hyperkalæmia. All potassium salts tend to irritate the stomach unless taken well diluted or as enteric-coated tablets.

The nitrate is the most diuretic of the potassium salts but is rarely used on account of side-effects. The acetate and citrate are oxidised to bicarbonates in the tissues and are thus remote alkalis: these salts and the bicarbonate are used to make the urine alkaline.

SODIUM SALTS. Since the tubule promptly reabsorbs  $Na^+$ , sodium salts have little diuretic action. In many situations where diuresis is required the administration of sodium salts is contra-indicated since much of the sodium is retained.

*Sodium sulphate* given orally is a purgative (p. 414); but when injected intravenously it will promote diuresis, for the capacity of the tubule for reabsorption of the sulphate ion is very low. It has been used to induce urine flow in cases of anuria, but this practice is now obsolete.

*Sodium bicarbonate* (dose, 1-4 G.). This sodium salt when taken in full doses 2- or 4-hourly produces an increased volume of alkaline urine. The tubules avidly reabsorb bicarbonate and diuresis only occurs when the reabsorptive system is overloaded. The renal loss of water induced by bicarbonate administration is never great. Continuous administration of large doses will lead to a systemic alkalosis.

*Sodium chloride* likewise is a poor diuretic. When a marked excess of chloride is present in the tubular urine an obligatory diuresis occurs. The oral administration of sodium chloride leads to little immediate diuresis. Thirst is induced and the water

ingested is eventually eliminated with the dose of salt, there being little or no reduction in body water. When hypertonic solutions are given intravenously a loss of body water occurs, since the chloride not reabsorbed will be excreted with an isosmotic quantity of water. During a water diuresis hypertonic saline can be shown to reduce temporarily the rate of urine flow by increasing the secretion of ADH; but this effect is obscured when a high rate of urine flow is occasioned by a large excess of chloride in the tubular urine.

*Uses of the Saline Diuretics.* The saline diuretics are of no value in the relief of œdema. The bicarbonates, the citrates and the acetates are given to produce an alkaline urine in pyelonephritis where they relieve symptoms promptly. Sodium bicarbonate and potassium citrate are commonly prescribed together—2 G. of each given 2-hourly until the urine is alkaline; thereafter 4-hourly for several days. Alkalinity of the urine is also necessary when chronic gout is treated with salicylates or cinchophen. These drugs promote the excretion of urates which are more soluble in an alkaline urine. Similarly, most sulphonamides and their acetyl derivatives are more soluble in an alkaline urine and when these drugs are being given an alkalinising mixture is recommended to prevent crystals forming in the renal tract (p. 501).

UREA (dose 5-15 G.) is the most powerful of the osmotic diuretics. When a full dose is taken by mouth it quickly appears in the glomerular filtrate in concentrations several times above normal. Some diffuses back into the blood stream but the rate of diffusion is too slow to permit the normal proportion (50 per cent) from being reabsorbed. The urea and accompanying water pass rapidly down the tubule and prevent the reabsorption of electrolytes which would otherwise be absorbed. Thus the increased urinary volume occasioned by a large dose of urea is brought about by the unabsorbed urea and unabsorbed salts restraining the reabsorption of an isosmotic quantity of water.

Urea is a bitter crystalline substance readily soluble in water. It is given dissolved in water and flavoured with fruit juice. To be effective as a diuretic 20 G. require to be given several times daily.

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In some patients such doses induce nausea and vomiting. It may be given as a diuretic in nephrosis where it is sometimes effective.

THE DIURETIC SUGARS are sucrose and mannitol. Glucose is also diuretic when its concentration in the glomerular filtrate exceeds the reabsorptive capacity of the tubule. When hyperglycæmia is present as in diabetes mellitus or following intravenous infusion of glucose, diuresis will occur from the unabsorbed glucose holding water osmotically within the tubular lumen. Sucrose and mannitol are more effective diuretics than glucose. They are not metabolised by the tissues, are readily filtered by the glomerulus and are very sparingly reabsorbed. For diuretic purposes they require to be given *intravenously*. Like urea the diuretic sugars promote an increased excretion of electrolytes.

*Uses.* Despite their action in promoting renal water loss, these sugars are rarely used to produce diuresis. They are of value in the relief of cerebral oedema. Hypertonic solutions given intravenously act osmotically to draw water from the tissues into the blood stream. In practice dextrose (50 ml. of a 50 per cent solution is always used; the intravenous injection of sucrose solution was abandoned when it was shown to produce degenerative changes (foamy swelling) of the tubular cells in the kidney. Since hypertonic dextrose solution causes a temporary expansion of the blood volume it can be used in an emergency to treat circulatory collapse but it is inferior to plasma or whole blood. The non-toxic mannitol is used as an alternative to inulin for the measurement of glomerular filtration rate.

ACID DIURETICS. Certain salts of ammonium and calcium have a diuretic effect by virtue of their ability to induce an acidosis. The most commonly used acidifying diuretic is ammonium chloride which is effective and safe when properly used. Ammonium nitrate and calcium chloride are less commonly used.

*Ammonium chloride* is rapidly absorbed from the intestine and in the liver  $\text{NH}_3$  is utilised to form urea by interaction with  $\text{H}_2\text{CO}_3$ . The HCl liberated lowers the alkali reserve since it

reacts with the  $\text{NaHCO}_3$  of the plasma to form  $\text{NaCl}$ . An acidosis is thereby produced since the ratio  $\frac{\text{NaHCO}_3}{\text{H}_2\text{CO}_3}$  is decreased.

*Calcium chloride* produces acidosis chiefly by reacting with the  $\text{NaHCO}_3$  of the digestive juices. The insoluble calcium carbonate formed is excreted in the fæces; the sodium chloride is absorbed. The net result is a reduction in the amount of sodium bicarbonate returned to the plasma from the bowel. This causes a fall in the alkali reserve and tends to produce an acidosis.

In the early stages of an acidosis increased excretion of water and fixed base (particularly Na) occurs, but as the acidifying agent accumulates the acid-base equilibrium is restored by the kidney and the diuresis and sodium loss cease. The renal response to acidosis is to conserve base by secreting a more acid urine and by forming  $\text{NH}_3$  from amino acids. In this way basic ions are returned to the plasma to restore acid-base balance. It takes several days for the compensatory processes of the kidney to be fully operative and it is during this lag period that acidifying agents cause a loss of sodium and water.

Ammonium Chloride (dose 0.3-4 G.) is given in a mixture or as tablets. It has a salty taste which is well disguised by Liquid Extract of Liquorice. Ammonium chloride tends to cause gastric irritation and should be taken well diluted with water or as enteric-coated tablets. Even with these precautions some patients cannot tolerate it. Calcium Chloride (dose 0.6-2.0 G.) is also irritant and is less commonly used. When prescribed it should be given as a mixture flavoured liberally with syrup of orange and preferably after food or a drink of milk.

*Uses as diuretics.* Since the diuretic effect of acidifying salts is limited to the first few days of therapy, they are unsatisfactory as the sole agents for the relief of œdema. They are, however, valuable supplementary diuretics for use in association with mersalyl. If mersalyl fails to produce a satisfactory diuresis in cardiac œdema, the cause is usually a deficiency of chloride in the tubular urine. By increasing the chloride load ammonium chloride restores the effectiveness of mersalyl (see p. 35). It is given in

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2 G. doses after food 4 or 5 times daily. Advanced renal disease is a contra-indication for the use of ammonium chloride. When the tubules are no longer capable of maintaining acid/base equilibrium the administration of an acid salt will cause a dangerous acidosis.

### CATION EXCHANGE RESINS

Cation exchange resins prepared in such a way that they promote the excretion of sodium in the fæces, have recently been introduced as an adjuvant measure to combat œdema.

Chemically the resins are polystyrene sulphonate or carboxylate, and for the removal of  $\text{Na}^+$  they have as exchangeable cations  $\text{H}^+$ ,  $\text{NH}_4^+$  or  $\text{K}^+$ . When in the intestine, the cations of the resin are given up and the sodium of the intestinal contents becomes attached to the resin and excreted in the fæces. For each  $\text{Na}^+$  adsorbed by the resin, a  $\text{H}^+$  or  $\text{NH}_4^+$  or  $\text{K}^+$  is added to the intestinal fluids. An acidosis is caused by the absorption of  $\text{H}^+$  or  $\text{NH}_4^+$ . Since the resins have a greater affinity for  $\text{K}^+$  than, for  $\text{Na}^+$ , part of the resin administered contains  $\text{K}^+$  as cation to diminish the tendency to potassium depletion. A useful preparation is "Kationium" which has 75 per cent of its cation as  $\text{NH}_4^+$  and 25 per cent as  $\text{K}^+$ .

The capacity of such a resin to remove sodium is limited. It is necessary to give large doses, 45–60 G. per day, and even this quantity does not remove all the sodium of a normal diet. When the diet, however, contains about 2 G. NaCl—and such a diet is barely palatable—the large dose of resin removes most of the sodium in the food and some from the intestinal secretions.

The diuresis induced by a cation exchange resin is slow in onset. The gradual faecal loss of sodium reduces the osmotic pressure of the plasma electrolytes and thus causes a water diuresis. In addition the  $\text{NH}_4^+$  form, acting like  $\text{NH}_4\text{Cl}$ , induces an acidosis in which renal loss of sodium occurs—particularly if therapy is intermittent.

*Uses.* Cation exchange resins are employed in association with a low salt diet as adjuvant therapy in combating the œdema of cardiac failure and nephrosis. In the latter condition renal func-

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tion must be carefully assessed before treatment is begun. When renal function is poor the administration of these agents leads to a dangerous uncompensated acidosis.

*Side-effects.* The hazards of resin therapy include potassium depletion, acidosis and hypocalcæmia. Close observation of the plasma electrolytes is therefore necessary. Gastric irritation is occasionally observed and in the elderly constipation may be troublesome. Some patients find the bulkiness of the resin (15-20 G. per dose) intolerable.

### PLASMA PROTEIN SUBSTITUTES

When the plasma protein level falls below 3 G. per 100 ml., œdema is likely to appear from the reduced colloidal osmotic pressure of the blood. This occurs in nephrosis when large quantities of albumin are lost through the kidney. The replacement of blood protein by plasma transfusion is impractical because the transfused protein rapidly disappears from the circulation and the electrolyte content of the plasma transfused is an additional burden to the kidney already having difficulty in excreting sodium. Salt-free human albumin concentrates are effective but prohibitive in cost. Plasma protein substitutes are therefore used. These are substances of large molecular size which when given intravenously increase the colloidal osmotic pressure of the blood. (Edema fluid thus moves into the vascular compartment and is excreted by the kidney.

The agents proposed as plasma protein substitutes are acacia, gelatin, dextran and polyvinylpyrrolidone. Acacia is no longer used since it is deposited in the liver and impairs hepatic function. Likewise polyvinylpyrrolidone, a water-soluble plastic, is partly stored in the muscles and skin. Suitable preparations of gelatin are not available in this country.

DEXTRAN is a polysaccharide formed by the action of a bacterium, *Leuconostoc mesenteroides*, on sucrose. It consists of many glucose units. As prepared for medicinal use it has an average molecular weight of around 70,000. A 6 per cent solution exerts an osmotic pressure approximately equal to that of normal

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plasma. Dextran is given intravenously. The rise in osmotic pressure of the blood attracts fluid from the extracellular space to increase the blood volume. This effect lasts for about 24 hours. When there is œdema due to hypoproteinæmia a marked diuresis may ensue. Much of the dextran is excreted by the kidney but the larger molecules slowly leave the blood stream and are metabolised in the tissues over a period of weeks. Dextran has antigenic properties and the reactions seen are allergic in type—urticaria, fever, bronchospasm and joint pains.

*Uses.* The administration of dextran is one of the methods by which discharge of œdema fluid may be accomplished in nephrosis. It is given intravenously in courses of 5 daily infusions of 500 ml. of 10 per cent dextran in 5 per cent dextrose solution. A 6 per cent solution of dextran in physiological saline may be used as an expedient to expand the blood volume in acute hæmorrhage and shock when whole blood or plasma is not available. Caution in the use of dextran is necessary when there is evidence of cardiac insufficiency.

*Summary of the Uses of Diuretics for Cardiac Œdema.* Not every patient with cardiac œdema requires a diuretic. Many mild and moderate cases respond satisfactorily to bed rest, a low salt diet and digitalis (p. 291). If a diuretic is necessary mersalyl is the first choice. When its action begins to wane in the presence of persistent œdema, the use of ammonium chloride often restores the diuretic response. Another method is to alternate acetazolamide with mersalyl, a period of 2 days elapsing between the use of each drug. When all the above measures fail intravenous aminophylline may be given in association with mersalyl provided the serum electrolytes are normal. A cation exchange resin may be used as an alternative to ammonium chloride. The resin permits a more palatable diet to be taken but it brings its own problems in management.

For the relief of *œdema in nephrosis* several agents are available: dextran which acts by raising the colloidal osmotic pressure of the blood; a cation exchange resin which limits sodium absorption from the intestine; mersalyl which prevents the reabsorption of



sodium in the glomerular filtrate, and adrenal steroids which also promote the renal loss of sodium in a way not fully understood. None of these drugs affects the essential disease process in the kidneys. The choice of drug for the individual patient depends on many factors: the degree of impairment of renal function, the age of the patient, the biochemical facilities available and the experience and preference of the physician. For many patients a trial of each drug in turn may be necessary.

## ANTIDIURETICS

Drugs may cause oliguria by lowering the glomerular filtration rate or by increasing the specific reabsorption of water by the renal tubule. Those drugs which cause hypotension are capable of reducing glomerular filtration and some of these, e.g. hexamethonium, may cause oliguria or anuria when given in overdose. A reduced urine volume brought about by increased tubular reabsorption of water is due only to the action of the antidiuretic hormone (ADH), *vasopressin*. This hormone is released from the neurohypophysis in response to the need to conserve water, the physiological stimulus being an increase in the osmotic pressure of the plasma electrolytes. Certain drugs such as morphine, phenobarbitone, nicotine and dimercaprol cause a release of ADH. With the exception of nicotine which may be used to test the integrity of the neurohypophyseal system, the antidiuretic effect of these drugs has no application in clinical practice.

**VASOPRESSIN.** Vasopressin and oxytocin, the posterior pituitary hormones, are polypeptides elaborated in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior lobe. They are extracted from the posterior lobes of oxen and other mammals, and separated by fractionation. Each is biologically standardised against the international standard. The actions of oxytocin are discussed in Chapter 13.

Injection of Vasopressin is a sterile aqueous solution containing 20 units of vasopressin per ml. The dose is 0.25–0.75 ml. (5–15 units) given by subcutaneous or intramuscular injection. If given by mouth vasopressin is destroyed by tryptic digestion in

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the intestine. Inactivation of vasopressin takes place in the liver and kidney. If large doses are given some is excreted in the urine.

*Actions.* The main effect of ADH is to produce a more concentrated urine. This is brought about by the action of the hormone in promoting the reabsorption of water without electrolyte ("free" water) in the distal part of the renal tubule. In health about 5 litres of "free" water are reabsorbed every 24 hours. In diabetes insipidus which is caused by a deficiency of ADH such water is excreted, giving rise to polyuria and thirst.

The renal tubules are exceedingly sensitive to the antidiuretic effect of vasopressin. As little as 2 milliunits given intravenously can be shown to reduce temporarily a water diuresis in man. A dose of 1 or 2 units injected subcutaneously is antidiuretic for 2 or 3 hours. When large doses of 5 to 15 units are given not only is the renal effect prolonged for 4 to 8 hours but certain smooth muscle tissues in the body are stimulated. This action is a direct one on the muscle fibre. There is intense vasoconstriction as shown by pallor of the face and diminished amplitude of the pulse. Constriction of the coronary arteries affects the action of the heart. If, through disease, the coronary arteries are already narrowed, anginal pain is likely to occur. Despite the overall pressor effect the blood pressure does not rise, partly because of depression of the myocardium and partly on account of reflex slowing of heart rate.

The smooth muscle of the intestine is stimulated causing increased peristalsis especially in the colon: intestinal colic is usually followed by evacuation of the bowel. In non-pregnant women uterine cramps may be experienced. These smooth muscle effects of vasopressin last for about 30 minutes.

*Uses.* The main therapeutic use of vasopressin is for the treatment of diabetes insipidus—a condition in which the endogenous production of the hormone is diminished or has ceased completely. Vasopressin Injection when given in doses insufficient to stimulate smooth muscle (1–2 units) has an-antidiuretic effect for 2–3 hours only and in the severe case frequent administration is required to abolish thirst and restore urine volume to normal.

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A more satisfactory preparation is a depot form of vasopressin from which ADH is slowly liberated to exert its renal action for 48 hours or more. Such a preparation is vasopressin tannate suspended in arachis oil ("Pitressin tannate" in oil). This is given intramuscularly in doses of 2-5 units (0.4-1.0 ml.) every second or third day. Side-effects are rarely encountered since the level of hormone in the blood does not greatly exceed physiological limits. Although vasopressin is absorbed through the nasal mucosa its use as a snuff is not a satisfactory form of treatment save in mild cases.

Vasopressin provides a convenient means of testing the concentrating power of the kidney. The specific gravity of the urine is measured at one hour and at two hours after 5 units of Injection of Vasopressin have been given intramuscularly. Vasopressin has been employed as a diagnostic test for epilepsy. Water retention which in epileptic subjects provokes EEG changes and sometimes convulsions, is achieved by giving over many hours simultaneous doses of water by mouth and vasopressin by subcutaneous injection.

The uses of vasopressin arising out of its stimulant action on smooth muscle are few. As a pressor agent in hypotension it is harmful since constriction of coronary arteries occurs. It may be employed to expel gas from the bowel prior to cholecystography. For post-operative intestinal atony and meteorism vasopressin is occasionally employed in association with neostigmine.

## TUBULAR BLOCKING AGENTS

In the discussion on diuretics reference was made to the enzymatic systems which control tubular reabsorption of electrolytes. Active transport mechanisms are also concerned with the tubular reabsorption of organic compounds such as amino acids, glucose, vitamins, uric acid and many drugs. The system involved in the reabsorption of uric acid is depressed by several drugs—salicylates, cinchophen and probenecid. When one of these is given the excretion of uric acid in the urine is increased. They are thus used in the treatment of chronic gout (p. 274).

Some organic acids are actively transported from blood into the urine by the cells of renal tubules. Examples are penicillin, carina-

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mide, para-aminohippuric acid (PAH) and diodone. These acids seem to share a common transporting system since when two are given together each depresses the tubular excretion of the other. They are thus competitive tubular blocking agents.

PAH and carinamide have each been used to depress the tubular excretion of penicillin, thereby prolonging effective blood levels following a dose of penicillin. These blocking agents, however, are themselves quickly excreted and to be effective require to be given in large and frequent doses. In practice it is easier to double the dose of penicillin.

PROBENECID represents an improvement on PAH and carinamide, for it is slowly excreted and has a more sustained blocking effect on tubular transport. It is filtered by the glomerulus and largely reabsorbed by the tubules. Its transport through the tubular cell involves an enzyme mechanism also utilised by uric acid, penicillin and some other organic acids. When probenecid is being reabsorbed it occupies preferentially the transport system to the partial exclusion of the other substances using the common route. It thus impairs the reabsorption of uric acid and the tubular excretion of penicillin. It does not interfere with the reabsorption of nutriment or electrolytes.

Probenecid is 4-(dipropylsulphamoyl) benzoic acid. In addition to its use to promote uric acid excretion in chronic gout (p. 274) it may be employed to maintain blood levels of penicillin (p. 439) and of para-aminosalicylic acid (p. 483).

## URINARY ANTISEPTICS

The ideal urinary antiseptic is a drug which when taken by mouth appears in the urine in concentrations sufficient to inhibit the growth of any bacterial agent infecting the renal tract. It should not readily induce drug-resistance in the organisms and should retain its potency irrespective of changes in the urinary pH. It should have no systemic side-effects, nor any toxic action on kidney tissue which might cause or aggravate impairment of renal function. All urinary antiseptics at present available fall short of this ideal in one way or another. This is the main reason

why the list of drugs which are available for the treatment of urinary tract infections is a long one. They will be described in the following order: (1) alkalinising salts, (2) sulphonamides, (3) mandelates, (4) nitrofurantoin, (5) antibiotics.

The organisms which infect the urinary tract are commonly of intestinal origin. *E. coli* is the most frequent single invader and at times is accompanied by *A. aerogenes* and *Str. faecalis*. Occasionally pyogenic cocci are the infecting agents. *Proteus* and *Ps. pyocyanea* which split urea to form ammonia are frequently found in chronic infections and are among the most difficult to eradicate. Tuberculosis of the renal tract and gonorrhœa have their own specific therapies which are considered elsewhere (p. 482 and p. 447).

### ALKALINISING SALTS

Alkalinising Salts are the bicarbonates and citrates of sodium and potassium. Their actions are described on p. 408. These salts are given to treat acute coliform infections which flourish in an acid urine. By alkalinising the urine abruptly, organismal growth is inhibited. The rapid relief of pain and frequency is attributable to reduction in acidity and diminished irritation of inflamed tissues. This is achieved by giving Sodium Bicarbonate and Potassium Citrate 2 G. of each 2-hourly until the urine is alkaline and thereafter 4-hourly to maintain the alkalinity. Excessive doses of these salts may cause diarrhœa. A copious fluid intake of at least 5 pints daily is also advised to ensure diuresis. Such a regimen relieves symptoms in acute pyelitis and in occasional cases the infection is cleared; but it cannot be depended on to *sterilise* the renal tract, and at the present time the alkalinising salts are commonly used in association with other antibacterial agents especially the sulphonamides.

In chronic, low-grade infections which commonly have a mixed flora, the alkalinising salts alone are of little value.

### SULPHONAMIDES

The sulphonamides comprise the most important group of urinary antiseptics. Their pharmacology is described in Chapter 15. In this section the discussion will be restricted to their role as antibacterial agents in the urine.

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Since the sulphonamides are largely excreted in the urine and are concentrated there, the urinary levels of free sulphonamides are many times those found in the blood. This is the basis of their use as antibacterial agents in the urine. In such concentrations they are commonly effective bactericides against coliform organisms, and some of the pyogenic cocci. *Proteus* organisms occasionally succumb but *Str. faecalis* and *Ps. pyocyanea* are resistant.

The sulphonamide drugs in common use have approximately the same antibacterial power and the same general, as opposed to renal, toxicity. Despite the varying percentage of free (i.e. active) drug which appears in the urine, all the sulphonamides listed in Table 2 are effective in 80 per cent of coliform infections of the renal tract. It seems likely there is a minimum concentration of free sulphonamide in the urine necessary for bacteriostasis, and levels above this are of value only when relatively resistant organisms are present. Further, when renal parenchyma is involved as in acute pyelonephritis the blood level of free sulphonamide is probably more important than the urinary level. Such considerations lead to the conclusion that there is little difference in antibacterial power between these drugs in renal tract infections. They differ however in the ease with which renal damage may occur from crystal deposition when their urinary concentrations pass the limit of saturation. Table 2 gives represen-

TABLE 2  
SULPHONAMIDES IN URINE

	Percentage in urine as free form	Solubility in urine mg. 100 ml. free form      acetylated at pH 5.5    7.5      5.5      7.5			
		5.5	7.5	5.5	7.5
<i>Sulphadiazine</i>	60-85	18	200	26	500
<i>Sulphamerazine</i>	40-65	35	160	38	275
<i>Sulphadimidine</i>	20-50	130	300	90	240
<i>Sulphasomidine</i>	85-90	280	450	20	40
<i>Sulphafurazole</i>	65-70	70	1,400	40	1,400
" <i>Trisulphonamide</i> "	60-90	160	400	140	1,000

tative figures for the solubility of the free and acetylated forms of the common sulphonamide drugs in acid and alkaline urines.

**SULPHADIAZINE.** In highly acid urine the solubility of both the free and acetylated forms of sulphadiazine is very low and in these circumstances crystal deposition is almost certain to occur. This hazard can be overcome by making the urine alkaline, when the solubility of free and acetylated forms is increased many times (Table 2). A minimum of 12 G. of sodium bicarbonate or equivalent daily is required to alkalinise an acid urine: the patient is instructed to test every specimen with litmus paper. A urinary volume of at least 2 litres is a further safeguard.

**SULPHAMERAZINE**, the monomethyl derivative of sulphadiazine is slightly more soluble in acid urine. In practice it has given rise to crystalluria more often than sulphadiazine and its use as a urinary antiseptic is not recommended.

**SULPHADIMIDINE** is commonly regarded as one of the safest of the sulphonamides. Having a low systemic toxicity it is also much more soluble than sulphadiazine in acid urine and thus renal damage does not commonly occur. Since it is acetylated to a greater extent than other sulphonamides a small proportion of the active drug appears in the urine; nevertheless, bacteriostatic concentrations are readily obtained. Alkalinising salts are commonly prescribed with sulphadimidine not only as a safeguard against crystalluria but also because they increase the urinary concentration of sulphonamide. Alkaline salts by depressing the tubular reabsorption of a sulphonamide promote its renal excretion. There is also some evidence that sulphonamides are more active in an alkaline medium when their ionisation is increased; but the importance of this in relation to bacteriostasis has been doubted.

**SULPHASOMIDINE** ("Elkosin"), an isomer of sulphadimidine, has two valuable features: 90 per cent of the drug which appears in the urine is in the active form and this free drug is highly soluble in both acid and alkaline urine (Table 2). Alkalinising salts are rarely required. Although the acetylated form is very sparingly

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soluble, crystal formation rarely occurs. This is because the amount of the acetyl form in the urine is very low (10 per cent) and its solubility is increased in the presence of the free drug.

**SULPHAFURAZOLE** ("Gantrisin"). Both the free and acetylated forms of sulphafurazole are very soluble in all save highly acid urines. It is thought, both on experimental and clinical grounds, to be the sulphonamide with the lowest renal toxicity.

**SULPHONAMIDE MIXTURES.** The principle underlying the use of a mixture of several sulphonamides rather than one is described on p. 507. The advantage gained is a marked increase in solubility of free and acetyl forms in both acid and alkaline urine. The mixture commonly used in this country consists of 3 parts each of sulphathiazole and sulphadiazine with 2 parts of sulphamerazine. Trisulphonamide ("Sulphatriad") tablets contain 0.5 G. total sulphonamide.

*Use of the Sulphonamides in Renal Tract Infections.* A cure rate of 80-90 per cent is to be expected in uncomplicated coliform infections when a sulphonamide is used. A high fluid intake is an important part of the treatment, for when the urine volume is 2 litres or more there is not only less chance of crystal formation but the antibacterial action of the sulphonamide is assisted by dilution of the bacterial inoculum. Regarding the selection of a sulphonamide, there is little to choose between the sulphonamides described above with the exception of sulphamerazine. When sulphadiazine is given alkalinising salts are imperative. With the others there is less need for alkali, but when the urinary pH is low (5.5) it is safer to give alkali or to use sulphasomidine. In brief, alkalinisation of the urine is nearly always valuable in giving rapid symptomatic relief; it enhances the effectiveness of the sulphonamides used in urinary tract infections; and therapeutic doses of alkalis are never harmful. When renal tissue is involved as in pyelonephritis full systemic doses of sulphonamides (p. 505) are required for 2-3 days until fever, loin pain and dysuria have disappeared; thereafter for a further week 1 G. is given 6-hourly. In general it is good practice to give full



doses of sulphonamides on the first day of treatment of an acute infection. This applies also to urinary tract infections especially when the parenchyma of the kidney is affected, but in view of the high concentration of sulphonamide in the urine, the dose can be reduced to 0.5 G. or even 0.25 G. 6-hourly on the second or third day—when the acute symptoms have usually subsided. To prevent urinary infection following surgical operations on the genito-urinary tract or when bladder drainage by catheter is necessary, a sulphonamide in 1 G. doses 8-hourly is given. A patient receiving a sulphonamide must be closely observed for toxic side-effects. These are described in Chapter 15.

*The Mandelates.* The mandelates were developed as urinary antiseptics following the observation that  $\beta$ -hydroxybutyric acid which is excreted in the urine when a ketogenic diet is given, has a powerful inhibitory action on the growth of organisms in the renal tract. This acid is metabolised when given orally but another simple hydroxy acid—mandelic acid—is excreted unchanged in the urine and is equally effective as a bacteriostatic. Certain requirements must be met before its anti-bacterial action is evident: the pH of the urine must be between 5.5–5.5; the concentration of mandelic acid in the urine must be over 0.5 per cent; and the infecting organism must be susceptible. Most of the common pathogens in the renal tract are susceptible including *Str. faecalis*; but *Proteus* and *Ps. pyocyanea* which make the urine alkaline by splitting urea are unaffected by mandelic acid.

Mandelic acid is commonly prescribed as the ammonium salt. This salt acidifies the urine since  $\text{NH}_3$  is converted to urea in the liver and the “free” mandelic acid lowers the alkali reserve. The degree of urinary acidity thus obtained may not be sufficient for full bacteriostatic action and not uncommonly it is necessary to give ammonium chloride (p. 667) to reduce the urinary pH to below 5.5. To obtain a satisfactory concentration of mandelic acid in the urine it is essential to restrict fluids so that the urine volume is under 1.5 litres per day. Ammonium mandelate, a white crystalline powder, is given as a mixture flavoured with Liquid Extract of Liquorice BP. The dose is 3 G. 4 times daily for a period of 2 weeks. Since it tends to cause gastric irritation it is

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taken after meals, well diluted in water. The sparingly soluble calcium mandelate may be given in tablet form or in a suspension. It is less irritating than the ammonium salt and has the same tendency to acidify the urine.

HEXAMINE MANDELATE ("Mandelamine") is claimed to be more powerful and less irritant than the other mandelates. In acid urine both fractions—the hexamine (see below) and the mandelic acid—exert an antibacterial effect. It is given in 1 G. doses 6-hourly.

*Side-effects.* In addition to gastric irritation the mandelates may cause diarrhoea and microscopic hæmaturia but these are rare. When renal function is impaired, a severe acidosis may result from retention of the mandelate: this is the chief drawback to using the drug.

*Uses.* A mandelate may be used for uncomplicated coliform infections of the renal tract but it is inferior to the sulphonamides and more liable to cause side-effects. The main indication for prescribing mandelates is a *Str. faecalis* infection of the urinary tract—a condition which responds poorly to sulphonamides (see also Antibiotics).

*Hexamine*, a condensation product of ammonia and formaldehyde, was formerly used as a urinary antiseptic. In an acid urine it liberates formaldehyde which, in non-irritant concentrations, is a poor antiseptic.

*Nitrofurantoin.* Certain substituted nitrofurane compounds have an antibacterial action by interfering with the respiratory enzymes of bacteria. One such compound, nitrofurantoin, is used as a urinary antiseptic. When taken by mouth about 40 per cent of it appears in an active form in the urine; the remainder is metabolised in the body. It affects a variety of organisms among them being the common pathogens in the renal tract. Coliform bacilli and pyogenic cocci are readily susceptible and at times *Str. faecalis*, *Proteus vulgaris* and *Ps. pyocyanea*. The antibacterial action of nitrofurantoin is not dependant on the urinary pH. On a weight

basis it is much more potent than the sulphonamides, an effective urinary concentration being 10 mg. per 100 ml. Such a level is obtained in the adult by giving 100 mg. 5 times daily. Since with high dosage nausea and vomiting are commonly experienced, it is recommended that the daily dose be computed on the basis of the patient's weight—5–10 mg. being given per Kg. body weight. If side-effects occur a reduction in dose is indicated.

Experience with nitrofurantoin is not yet extensive. So far, no serious toxic effects have been reported but drug rashes may appear. Its place as a urinary antiseptic remains to be defined. Reports of its use in chronic infections, especially mixed infections, indicate that it is a valuable addition to the group of urinary antiseptics. Micro-organisms insensitive to sulphonamides, mandelic acid and the antibiotics may be eradicated by its use. Nitrofurantoin ("Furadantoin") is available as 50 mg. tablets.

**ANTIBIOTICS.** Most antibiotics exert an antiseptic action in the urine; none, however, is universally effective. Apart from urinary stasis caused by stone or anatomical abnormality, failure may be due to the natural resistance of the infecting organism or to insensitivity induced by previous exposure to an antibiotic. Useful information on the sensitivity of the organism can be obtained from the bacteriologist, but sensitivity tests do not invariably reflect *in vivo* susceptibility. Nevertheless, since antibiotics are expensive it is reasonable to know before they are prescribed that their use appears to be justifiable. In general antibiotics are reserved for those cases of urinary tract infection which have not responded to the sulphonamides, mandelates and nitrofurantoin.

*Penicillin* appears promptly in the urine and very high concentrations are obtained. Very occasionally a coliform infection yields to penicillin but the common urinary pathogens are usually resistant. *E. coli* secretes penicillinase which destroys penicillin. When the infecting organism is a penicillin-sensitive pyogenic coccus a course of penicillin quickly cures.

*Streptomycin* is excreted by the kidney largely in an unchanged state and urinary levels of 200–2,000  $\mu$ g. per ml. are found when

## PHARMACOLOGY OF RENAL FUNCTION

0.5-1.0 G. are given 6- or 8-hourly. With such concentrations simple infections with *E. coli* or *A. aerogenes* are eradicated within 1 or 2 days. Some strains of *Str. faecalis*, *Proteus* and *Ps. pyocyanea* are susceptible. Occasionally resistant strains rapidly emerge during treatment, especially when the infection is heavy or mixed. The ease with which drug resistance can be induced is an important drawback to streptomycin therapy. Alkalinity of the urine greatly enhances the bactericidal power of streptomycin and increases three-fold the chance of sterilising the urine. To ensure a suitable pH for maximal antibacterial activity, 2 G. each of sodium bicarbonate and potassium citrate should be given 4-hourly. Streptomycin sulphate is given intramuscularly 0.5-1.0 G. 8-hourly for 4 to 5 days. In such a short course the risk of serious toxic effects (p. 452) is slight. Nevertheless, the risk is much increased when pyelonephritis is so severe that impairment of excretion results in cumulation of the antibiotic.

*The Tetracyclines.* Although the tetracyclines are unstable substances in the body and are excreted slowly by the kidney, concentrations are readily obtained in the urine which are bactericidal to the common pathogens of the renal tract. A dose of 1 G. daily in divided doses commonly sterilises the urine infected with *E. coli* or *A. aerogenes*; *Str. faecalis* is occasionally eradicated, but *Proteus* is not usually susceptible and frequently replaces the original micro-organism during the course of treatment. The use of alkalinising salts is contra-indicated with tetracyclines which are unstable in an alkaline medium. Bacterial resistance to the tetracyclines does not readily occur—affording an important contrast with streptomycin therapy. A course of treatment consists of 0.25 G. orally every 6 hours for 7-10 days. Tetracycline rather than oxy- or chlortetracycline should be used since a higher proportion of the dose appears in the urine and side-effects are less common (p. 460).

*Chloramphenicol.* Only 10 per cent of the dose of chloramphenicol appears in active form in the urine. However it readily brings a coliform infection under control. Coccal infections are not susceptible. The reaction of the urine is immaterial: it differs

from streptomycin and the tetracyclines in being active through a wide range of pH. Since the use of chloramphenicol carries a remote risk of grave injury to bone marrow (p. 467), it should not be prescribed as a urinary antiseptic unless the indications are clear. These are (1) insensitivity of the infecting organism to other urinary antiseptics and (2) sensitivity of the organism to chloramphenicol. The dose to be given is 0.5 G. orally, 6-hourly for 2-3 days and half this amount for a further 5 days.

### THE CHOICE OF A URINARY ANTISEPTIC

For renal tract infections due to coliform organisms a sulphonamide is the agent of choice on the grounds of effectiveness, ease of administration, low cost and—when due precautions are taken—low toxicity. The concomitant use of alkalinising salts (p. 54) is advantageous. When the infection fails to yield to a sulphonamide, bacteriological examination should be carried out together with tests of the sensitivity of the pathogen to the various urinary antiseptics. The persistence of a sulphonamide-sensitive organism after a course of sulphonamide should raise the possibility of a structural lesion in the renal tract: investigation may reveal the presence of calculus, hydronephrosis, tumour, etc.—each calling for the appropriate surgical procedure. For infections due to a sulphonamide-resistant organism, the choice of drug depends not only on the type of bacterium but more important on its sensitivity to the antibacterial agents. When such information is not available, a sulphonamide-refractory infection should be treated by nitrofurantoin which has a broad range of activity. The mandelates may be given for infections due to *Str. faecalis*; they are useless for infections caused by *Proteus* and *Ps. pyocyanea*. The antibiotics are best reserved for those cases in which other urinary antiseptics have failed.

When poor kidney function (due to intrinsic renal failure or congestive cardiac failure) is associated with a renal tract infection, due regard must be paid to the diminished excretion of the urinary antiseptic used. The higher blood levels of a sulphonamide in renal insufficiency may lead to increased toxic effects and only half the recommended doses (p. 505) may be tolerated. In conges-

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tive cardiac failure the alkalinising salts of sodium are contra-indicated. In these circumstances the sulphonamide of choice is sulphasomidine. Mandelates must not be given when renal function is poor, since retention of the mandelate leads to an uncompensated acidosis. Caution is also necessary with streptomycin which may show toxic effects when its rate of excretion is diminished.

## CHAPTER 3

# HÆMATINICS, HUMAN BLOOD, AND PLASMA

### HÆMATINICS

THE development and health of living tissues cannot be maintained unless a large variety of chemical substances are present and readily available to the cells. This general statement applies to the histogenesis of the red blood cells. Theoretically, therefore, many types of anæmia attributable to specific deficiencies could occur. In fact, however, there are relatively few-- those associated with lack of (a) *iron*, (b) *cobalamins* and (c) *folic acid*. These substances are collectively known as the hæmatinics. Under physiological conditions they are already present in the tissues of the organism and by the operation of self-regulating mechanisms (which are still obscure) they exist in optimal concentration. It is therefore not surprising that when supplements of these hæmatinics are fed to a healthy man, they confer no additional benefits. On the other hand, when a hæmatinic is given in the treatment of a patient whose anæmia is directly attributable to lack of that substance, the hæmopoietic action is remarkable.

### IRON

**ABSORPTION, FATE AND EXCRETION.** Iron is an essential constituent of the human body: the total iron content of the adult is 4.5 G. Of this 60-70 per cent is present in the red cells as hæmoglobin, the iron-containing pigment by which oxygen is carried; 10-15 per cent is incorporated in other body tissues especially skeletal muscle, which contains approximately another 5 per cent in the form of myoglobin. The tissue iron fraction includes the iron present in the enzymes, especially in the cytochrome and catalase systems. The remainder (15 per cent) is accounted for almost entirely by the iron stores in the reticulo-

endothelial system. Apart from a small and unavoidable iron loss, no mechanism exists for *excretion* of this metal; but there is a controlled *absorption* mechanism which ensures that the body stores are normally maintained at a constant level, absorption taking place only to make good any depletion of the reserves. Iron is "accepted" by this mechanism in the ferrous state.

Iron-rich foods in the diet (red meat, liver, egg yolk, wholemeal cereals and green vegetables) contain mainly ferric iron. Of this daily intake only about 10-15 mg. is ionisable, a point of great practical importance as only the ionisable fraction (10-15 mg.) is available for absorption. Ionisation takes place in the stomach under the influence of gastric hydrochloric acid, a pH lower than 5 being essential for adequate dissociation. The ferric ions are reduced to ferrous by reducing substances in the food—mainly ascorbic acid, protein sulphhydryl groups and fatty acids. The ferrous ions thus produced pass into the small bowel where they are available for absorption through the operation of a special mechanism in the intestinal mucosa. While this absorption may take place at any level, the acidity required to produce an adequate supply of ferrous ions is found only in the duodenum and upper jejunum, and iron absorption is largely confined to this part of the intestines. Much of the ionisable iron is rendered unavailable for absorption as it forms insoluble complexes with other dietary constituents such as phosphates.

The ferrous ions enter the epithelial cells where they combine with an iron-free protein, apoferritin, converting it to ferritin. When all the apoferritin in the epithelial cell is converted to ferritin, no further iron can be absorbed. As the demand for iron arises, the metal is removed from the ferritin of the epithelial cells and carried in the portal blood stream to the liver and also to the other iron depots—situated in the reticulo-endothelial tissues, notably in spleen and bone marrow. Iron in these stores is available for hæmopoiesis and for incorporation into body tissues. As iron is removed from the ferritin of the mucosa apoferritin is re-formed, and further absorption can then take place. Should no iron be required, the mucosa remains saturated with ferritin and absorption is prevented. In this way the harmful effects of excessive concentrations of iron in the tissues are avoided.



Though the iron liberated from effete red cells and broken-down tissues is preserved in the iron stores a continual iron loss takes place in two ways: iron being an essential constituent of all tissues some is lost by desquamation of skin, hair and alimentary epithelium; there is also a small loss in the urine. These unavoidable losses amount to 1.0-1.5 mg. daily. In the adult female an additional 10-40 mg. of iron is lost each month at menstruation. During pregnancy the growing foetus requires about 500 mg. iron, and iron is also required to replace postpartum blood loss. This often warrants the administration of an iron supplement to the mother, either as foodstuffs rich in iron or as a pharmaceutical preparation. In lactation there is a loss of up to 1.5 mg. per day in the milk. The growing child requires an extra 1.5 mg. of iron each day to supply haemoglobin for an increasing red cell mass, and tissue iron for an increasing muscle mass. These requirements are balanced against the 10-15 mg. of iron supplied by the diet each day. Of this quantity normally only 1.0-1.5 mg. is absorbed, and though this amount increases when iron is required it rarely exceeds 25 per cent of the available iron, the remainder probably being lost in insoluble complexes in the faeces. The iron balance of the adult male is satisfactory, but during growth and the reproductive years of life iron deficiency may readily occur, particularly if the diet is deficient. Chronic blood loss quickly produces iron deficiency, a loss of 10 ml. daily being equivalent to an iron loss of 2.5 mg. per day- which is rather more than can readily be replaced from the diet.

Iron deficiency prevents adequate haemoglobinisation of the red cells and produces an anaemia in which the number of the red cells is only slightly reduced, but in which the *haemoglobin content* is diminished. The effect on the marrow function is slight and it becomes apparent only at the late stages of erythropoiesis. In iron deficiency of long standing, signs of deficiency in other tissues may also be found. These usually occur later than anaemia and include glossitis, stomatitis, dryness of the skin and hair, and koilonychia. There are no other conspicuous effects of iron deficiency. As is shown by the iron balance, iron deficiency in the adult male and in the post-menopausal woman is a symptom of blood loss and is not a diagnosis or disease in its own right. In

## HÆMATINICS, HUMAN BLOOD, AND PLASMA

women in the reproductive years iron deficiency readily arises with even minimal dietary deficiency.

**PHARMACOLOGY.** When pharmaceutical preparations of iron are prescribed for patients suffering from iron-deficiency anæmia, the effects of the metal appear to be identical with those of the iron contained in food. The description of an iron salt as a “drug” is based on the fact that it is given to a *patient*—whose disability is attributable to the pathological state of hypochromic anæmia. This matter is of some importance in relation to preserving the distinction between a *food* and a *drug* (p. 1). The contrast is valid, notwithstanding the fact that the fate of iron salts when given therapeutically as hæmatinics is a physiological phenomenon and not strictly a “pharmacological action”. In this context it may be said that pharmacologically iron behaves as do other heavy metals. Soluble iron salts precipitate protein, and the effect is *astringent* or *corrosive* according to circumstances which are discussed briefly elsewhere (p. 579). The deliberate use of iron salts as astringents and corrosives is obsolete. This action does occur, however, as a side-effect of oral iron therapy: irritation of the gastric mucosa by iron salts may cause nausea and even vomiting; and astringency in the bowel often causes constipation but occasionally diarrhœa may occur.

**TOXICOLOGY.** 1. *Local Reactions in the Alimentary Tract.* In overdose, especially in children, iron salts cause acute toxic enteritis and this may be fatal. In smaller doses the astringent action may cause considerable irritation resulting in colic and diarrhœa. As already stated, a few patients experience nausea and constipation, even after average therapeutic doses, and these symptoms are also attributable to mild astringency. If taken in fluid mixtures, iron may combine with sulphide ions in the mouth forming black iron sulphide which discolours the teeth. The same compound is formed in the intestine and this causes blackening of the stool. This may suggest gastro-intestinal bleeding, but whereas the stool that is black from iron sulphide has a matt lustreless appearance, the melæna stool is often intensely black and shiny like tar.

2. *Reactions Associated with Parenteral Administration.* Even iron preparations for parenteral use are irritant; pain usually occurs at the site of intramuscular injection, and venous thrombosis after intravenous injection is common. Should intravenous preparations leak into the subcutaneous tissues necrosis and sloughing may follow. *Subcutaneous* injection of intramuscular preparations causes severe pain, and also produces a permanent disfigurement by skin pigmentation. Sudden collapse and death has been reported after intravenous injection; this is attributed to the presence of a few free ferrous ions which contaminate the preparation. Sneezing, flushing of the face, headache and acute collapse are also found.

3. *Sensitisation Reactions to Parenteral Injections.* It is not usually the iron itself that evokes sensitisation but the substance with which it is combined, for example, the dextran in the intramuscular preparation. This is rare.

PREPARATIONS AND ROUTES OF ADMINISTRATION. I.  
*Oral Administration.* Since iron is absorbed from the intestine in the ferrous form, iron is best given as a ferrous salt. Many such preparations are available, but the cheapest and most effective is Ferrous Sulphate (tablets of 0.2 G., one thrice daily after food). If symptoms of gastro-intestinal irritation are troublesome alternative preparations such as Ferrous Gluconate or ferrous succinate (both tablets of 0.3 G., one thrice daily) should be tried. If a mixture is required, ferrous salts (which are unstable in solution) are not suitable and Ferric Ammonium Citrate should be used. This "scale" preparation is readily dissolved and is stable in solution. As the iron is present in the ferric form a much larger dose (2 G. thrice daily) is required to ensure absorption of an adequate amount of iron. In order to minimise gastro-intestinal irritation all oral iron preparations should be given after food. Therapy should be started with a small dose once daily, and full doses should be gradually reached over the course of three or four days. In this way tolerance is established. In an attempt to replenish the iron stores, therapy should be continued for at least one month after the hæmoglobin has been restored to normal.

2. *Intramuscular Injection.* An iron-dextran complex, "Imferon", is available, and is the preparation of choice for injection: 50 mg. of iron are contained in 1 ml. of solution which is administered deep into a large muscle mass, preferably the upper and outer aspect of the buttock. About half of the injected iron is permanently deposited in the regional lymph nodes and of each 250 mg. injected only 100 mg. becomes available for hæmopoiesis. This should produce a 4 per cent rise in the patient's hæmoglobin and doses should be calculated on this basis. The initial dose should not exceed 2 ml. but doses up to 5 ml. may be used. By giving three to five injections more than the calculated requirement, depleted iron stores can be replenished with certainty. As there is a risk of siderosis, the appropriate dose should not be greatly exceeded. Blood regeneration with parenteral iron preparations is no quicker than an optimal response to adequate oral therapy, and intramuscular iron should be reserved for patients who are genuinely intolerant of oral iron, or where there is malabsorption of iron.

3. *Intravenous Injection.* Saccharated iron oxides, "Iviron" and "Ferrivenin", are available for intravenous injection. They contain 100 mg. of iron in 5 ml. of solution, and should contain no free ferrous iron. The first injection should be of 20 mg. and no single injection should exceed 100 mg. These preparations are more toxic than intramuscular iron, both locally and systemically, and have no apparent advantage, save that the whole of the injected iron is available for hæmopoiesis.

*Cobaltous Chloride.* Cobaltous chloride, acting by an unknown method, produces even in the normal person a reticulocytosis with an increase in red cells and hæmoglobin. This increase, which is sustained only for the duration of therapy, is obtained also in some of the refractory anæmias and in the anæmia of advanced renal disease. Moderately good results are obtained with this form of therapy, but cobaltous chloride is highly toxic; at the moment its status in therapeutics awaits exact assessment.

CYANOCOBALAMIN (VITAMIN B<sub>12</sub>) AND FOLIC ACID

INTRODUCTION. Cyanocobalamin and folic acid are both necessary for the bio-synthesis of nucleic acids: they are therefore indispensable to normal nuclear maturation. The functions of cyanocobalamin and folic acid have not yet been fully defined. Nevertheless deficiency states have been recognised for many years: lack of cyanocobalamin and of folic acid is readily apparent in cells that are actively dividing; and even in tissues where mitosis is less active—notably in the skin and in the epithelium of the alimentary canal—significant changes may develop. Although signs of deficiency in other body tissues may not be apparent to the clinician, it is probable that all systems are involved, for the effects of both cyanocobalamin and folic acid on metabolic processes are not restricted to hæmopoietic tissue. Both substances are concerned in the same group of processes—in particular trans-methylation reactions.

Folic acid deficiency may produce a blood picture which is clinically indistinguishable from that of cyanocobalamin deficiency. Further, the immediate cytological response to appropriate specific therapy is apparently the same. It would appear, therefore, that folic acid and cyanocobalamin have much in common as regards their effect on hæmopoietic tissue. This illustrates how the process of maturation of the erythrocyte may be hindered by one of several deficiency states: the nature of the resulting anæmia indicates roughly the phase at which interference has occurred rather than the precise nature of the deficiency. Hence it is not surprising that cyanocobalamin deficiency and folic acid deficiency should result in similar hæmatological pictures. It must be emphasised, however, that this cytological response is only a part of what is needed therapeutically: the use of folic acid for the treatment of Addisonian pernicious anæmia greatly increases the risk of serious neurological complications (demyelinating lesions); on the other hand, adequate doses of cyanocobalamin in this disease provide comprehensive treatment—restoring the blood picture to normal, preventing the occurrence of neurological lesions and even abolishing the symptoms of peripheral neuritis

which are an almost invariable accompaniment to subacute combined degeneration of the cord.

As already stated, in man the most striking signs of cyanocobalamin deficiency and of folic acid deficiency are *haematological*; and in the abnormal blood picture produced, megaloblastic erythropoiesis is common to both. Megaloblastic change is seen in the active bone marrow where nuclear maturation is disordered and delayed, though there is no delay in hæmoglobinisation. Leucocyte and platelet production are also adversely affected, but the changes are not so obvious as those in the red cell series. As the abnormalities in the blood picture are common to both types of deficiency state, the final diagnosis depends on diagnostic procedures other than blood examination. The *cause* of the deficiency must also be demonstrated: this is nearly always possible, for the deficiency state is very rarely a *primary* disease. Only when a complete diagnosis has been made can rational therapy be given. Differentiation between Addisonian pernicious anæmia and folic acid deficiency anæmia does not usually present difficulty when a survey is made of all the clinical data. The accuracy of the diagnosis is subject to confirmation by means of a *therapeutic test*: there should be an unequivocal response to treatment in terms of a reticulocytosis (proportional to the severity of the anæmia), a sustained rise in the RBC and hæmoglobin readings, and reversion to normal of the white cells, platelets and bone marrow. If a preparation of known therapeutic potency has been used, absence of such a response makes the diagnosis untenable. In rare cases where the total clinical picture gives no strong lead in making a choice between cyanocobalamin and folic acid, it is advisable to make a therapeutic trial with cyanocobalamin first. This can do no harm, whereas the use of folic acid in the presence of cyanocobalamin deficiency is likely to produce a fulminating exacerbation of neurological symptoms and signs—notwithstanding an improvement in the blood picture.

#### CYANOCOBALAMIN—VITAMIN B<sub>12</sub>

*Source.* Vitamin B<sub>12</sub> is unique among all the substances essential for body function, first because it can be obtained only from animal sources, and secondly because it contains the toxic metal

cobalt. It is synthesised by bacterial action in the bowel of almost all animals when cobalt is present in the diet, but only in ruminants does this synthesis occur sufficiently high in the gut to permit absorption. Thus the flesh of ruminants—especially the liver, stomach, brain and skeletal muscle in which greatest concentration takes place—is the only important source of cyanocobalamin in the diet; and the first therapeutic preparations of the hæmatinic principle were made by extraction and concentration of animal liver. The preparations now used therapeutically are obtained as a by-product of the manufacture of streptomycin, for cyanocobalamin is formed in large quantity by the *Streptomyces griseus* during fermentation. The vitamin B<sub>12</sub> so formed is extracted in a very pure state at low cost.

*Chemistry.* Cyanocobalamin is the most frequently occurring of a group of compounds all of which possess similar metabolic activities. It is a red, needle-shaped, crystalline compound of molecular weight approximately 1,300; and it is unique among essential natural substances by virtue of the cobalt which it contains (4·5 per cent). Cyanocobalamin is soluble in water (1 in 80) to form a relatively stable solution which withstands autoclaving and keeps well. It is, however, destroyed by prolonged contact with heavy metals and oxidising agents.

*Physiology.* Vitamin B<sub>12</sub> in food is bound to proteins from which it is readily freed by proteolytic enzymes in the gut. Thereafter it is absorbed by a complex mechanism, requiring both the secretion of a mucoprotein by the stomach and a specific acceptor mechanism in the small bowel. The mucoprotein, the intrinsic factor of Castle, is secreted in man by the glands in the fundus of the stomach; in some animals, notably the pig, it is secreted by the pyloric glands. Intrinsic factor enters into a loose physico-chemical combination with cyanocobalamin, acting in a specific but unknown way to potentiate absorption which takes place in the small bowel. In the absence of intrinsic factor absorption of dietary vitamin B<sub>12</sub> ceases. After it has been absorbed, cyanocobalamin circulates in the blood stream bound to plasma protein. It is carried in the portal vein to the liver which is the main

site of storage. Some is also stored in stomach, skeletal muscle and kidney. The body store is large—of the order of 2,000 micrograms. Cyanocobalamin is the most potent of the vitamins, the daily requirement being only 1–2 micrograms. When the absorption mechanism is intact this amount is readily obtained from the diet. A prolonged deficiency state produces a characteristic syndrome which is, however, usually insidious in onset, as the large store of vitamin B<sub>12</sub> must be consumed before symptoms appear.

Cyanocobalamin has a wide variety of metabolic actions which are apparently unrelated, but it is probable that these are all expressions of a single, as yet unknown, fundamental action. The clinically important actions are those on nucleic acid metabolism and on myelination. Although cyanocobalamin plays a part in many enzyme systems, hæmatological or neurological signs are the earliest signs of deficiency; and in man, if there are no abnormalities in the nervous system or in the blood picture, signs of involvement of enzyme systems in other tissues have still to be demonstrated. The use of vitamin B<sub>12</sub> as a dietary supplement or as a “tonic” is irrational.

*Pharmacology.* Vitamin B<sub>12</sub> has no known pharmacological action: it is used only for its physiological action in the treatment of deficiency states.

*Toxicology.* Vitamin B<sub>12</sub> is obtainable in a chemically pure state, and is completely devoid of toxic effects. Sensitisation reactions occur very rarely, and these are due to contamination of the preparation, and not to cyanocobalamin itself.

*Absorption, Fate and Excretion of Therapeutically Administered Cyanocobalamin.* The cause of deficiency of vitamin B<sub>12</sub> is almost invariably failure of the normal mechanism for absorption, and when cyanocobalamin is used therapeutically it must be given parenterally. This is most clearly seen in Addisonian anæmia (“pernicious anæmia”) where gastric atrophy leads to a failure of intrinsic factor secretion and so prevents absorption of vitamin B<sub>12</sub>. Cyanocobalamin is non-irritant and is rapidly and com-



pletely absorbed from subcutaneous and intramuscular injection sites. The amount retained in the body depends on the ability of the plasma to combine with it, for the free cyanocobalamin in the plasma is rapidly excreted by the kidney. Thus renal loss increases with increasing dose; 7 per cent of a 50 microgram dose; 60 per cent of a 1,000 microgram dose.

The subsequent fate of the injected vitamin B<sub>12</sub> is not known. It is stored in the tissue depots. A very small quantity appears in the urine as degradation products. The intermediate steps in its metabolism are unknown as is the case with cyanocobalamin taken in the diet.

*Preparations.* Cyanocobalamin is dispensed in sterile solution in normal saline in concentrations of 50, 100, 250 and 1,000 micrograms per ml. It is administered by subcutaneous or intramuscular injection.

*Dose.* From the theoretical consideration of the daily requirements a very small dose would appear to be adequate, but in practice large doses must be used. For this there are two main reasons: (1) the clinical signs of deficiency, however mild, indicate a serious tissue depletion of vitamin B<sub>12</sub> and this should be corrected as soon as possible; (2) inadequate therapy exposes the patient to the risk of irreversible neurological complications. In view of these two considerations and the fact that cyanocobalamin appears to be devoid of toxic effects therapeutic doses should always err on the generous side. Various dose schemes are suggested, and a reasonable one appears to be 250 micrograms thrice in the first week of treatment, thereafter weekly till the hæmoglobin is restored to a normal level. Indefinite maintenance therapy is required and the dose given must be such as to keep the hæmoglobin at a normal level continuously. The quantity varies from patient to patient, and the dose required for the individual must be found by repeated blood examinations. Suboptimal maintenance therapy carries the hazard of neurological complication. When the blood picture has been restored to normal, the average requirement of vitamin B<sub>12</sub> appears to be 250 micrograms every third or fourth week.

## FOLIC ACID (PTEROYLGLUTAMIC ACID)

INTRODUCTION. Folic acid received its name because of its wide distribution in the leaves of green vegetables. One of its outstanding properties is its growth-stimulating effect on a variety of micro-organisms, and this was well known before its precise chemical structure had been determined. It is a conjugate of glutamic acid, para-aminobenzoic acid and pteridyl. The naturally-occurring folic acid usually has an excess of glutamic acid radicles in its molecule and in this form it has little activity. There are, however, tissue enzymes, the conjugases, which split off the excess glutamic acid and liberate free folic acid. There is a specific mechanism which controls the absorption of dietary folic acid (or its conjugates) from the small bowel. Thereafter it is stored in the liver and from this depot it is distributed to the tissues in amounts that are appropriate to the degree of metabolic activity. Before utilisation it is converted to folinic acid, a change involving reduction and formylation. For this conversion ascorbic acid is essential. The general nature of the action of folic acid, or rather the active form folinic acid, has already been described (p. 70); the action resembles that of cyanocobalamin, save that folic acid lacks the therapeutic value of cyanocobalamin in abolishing the symptoms of peripheral neuritis in subacute combined degeneration of the cord.

The preparations used therapeutically are synthetic. Folic acid is a yellow-orange powder without odour or taste. It is almost insoluble in water, though it may be dissolved in acids or alkalis. In solution it is relatively unstable, and as preparations for parenteral injection are difficult to make, they are no longer freely available. Folic acid given by mouth is well absorbed.

Dietary deficiency of folic acid is thought to be very rare in this country. The daily requirement of 0.1-0.2 mg. is readily obtained from a poor diet, and deficiency states are usually caused by a *failure of absorption*--as, for example, in the malabsorption syndrome and in tropical sprue. In these diseases, notwithstanding the difficulty in absorbing an adequate amount of folic acid from the diet, the much larger quantities given by mouth therapeutically result in satisfactory absorption and the benefits are soon apparent.

The fate of folic acid administered therapeutically is not known, but is presumed to be the same as that of dietary folic acid. A small part of the folic acid appears unchanged in the urine, and a still smaller part appears as folinic acid. As the dose of folic acid is increased the proportion excreted unchanged is also increased, but remains low. Elucidation of the mechanism of absorption of folic acid and its metabolism await the development of a satisfactory technique for the assay of folic acid in biological fluids.

Like iron and cyanocobalamin, folic acid is used for its physiological action in deficiency states, and has no apparent pharmacological action. Its beneficial action on the bowel in acute tropical sprue is probably only one facet of its physiological function.

Folic acid has no known toxic effects when it is employed in the treatment of folic acid deficiency. If it is used in the treatment of cyanocobalamin deficiency folic acid may precipitate irreversible neurological damage. Therefore, if the precise nature of the deficiency producing megaloblastic erythropoiesis is not known, cyanocobalamin should always be used first in a therapeutic trial.

Folic acid is dispensed in 5 mg. tablets for oral administration: the total dose varies from 5 to 30 mg. a day.

### LIVER EXTRACT

For many years injection of extracts of mammalian liver was the standard form of treatment in Addisonian anæmia. These extracts are active only by virtue of their content of cyanocobalamin, and now that standardised pure preparations of cyanocobalamin are readily available, liver extract should no longer be used. The cyanocobalamin content of liver extract is low and variable—and this is obviously a disadvantage. Again, however far purification of liver extract is carried, the final product for injection is inevitably contaminated with foreign protein, and this may prove to be a potent antigen (p. 519). Only in cases where a patient has been maintained in good health for many years with liver extract without developing sensitisation phenomena is it justifiable to use these preparations; and in these circumstances a highly purified form should be chosen.

## HÆMATINICS, HUMAN BLOOD, AND PLASMA

*Oral Preparations for use in Addisonian Anæmia.* Both cyanocobalamin and also liver extracts are offered for oral administration. Neither type of preparation has been shown to be a *reliable* form of maintenance therapy in Addisonian anæmia. The use of these preparations by mouth is therefore not recommended. These statements represent the generally accepted views of clinicians who have studied the matter, notwithstanding the fact that it is usually possible to demonstrate significant responses after the oral administration of these preparations. The essential point is that the demonstration of a pharmacological action does not necessarily provide proof of therapeutic efficacy—when the physician insists on an adequate definition of therapeutics. Similarly, preparations containing cyanocobalamin with added intrinsic factor derived from animal sources have not proved reliable in maintaining complete remission in pernicious anæmia; they should therefore not be used in the treatment of patients suffering from this disease.

## · HUMAN BLOOD AND DERIVATIVES

### WHOLE BLOOD AND CONCENTRATED RED CELLS

Human blood for transfusion is obtained from healthy donors: it is taken by an aseptic technique into an acid citrate-dextrose anticoagulant mixture. Immediately after collection it is cooled to 4° C. and refrigerated continuously at that temperature until just before it is used. It may be stored for 21 days without impairment of the survival of the cells after transfusion; but thereafter erythrocyte survival is poor, and blood more than 21 days old should not be used. Before whole blood is transfused, accurate grouping and cross-matching must be carried out. Transfusion of whole blood should normally be reserved for the treatment of patients with post-hæmorrhagic shock, severe post-hæmorrhagic anæmia, or anæmia not responsive to other measures. The hæmoglobin content of the blood transfused is not less than 66 per cent. Should an infusion containing more cells in a smaller volume of fluid be required, then “packed red cells” are available (the *Concentrated Human Red Blood Corpuscles* of the BP): 40 per cent of the supernatant plasma and anticoagulant is removed from

whole blood. The red cell content of the remaining "packed cells" is at least 5.5 million/cu.mm. Concentrated cells must be infused within 12 hours of preparation. They are used for transfusion to anæmic patients in circumstances which make it essential that there should be the least possible increase in the blood volume. There is a real danger of circulatory overloading if a single infusion of "packed cells" exceeds 500 ml.

### PLASMA

Plasma is used for infusion in oligæmic shock. It is obtainable either as citrated liquid plasma or as dried plasma. Both of these are prepared from a pool of supernatants separated from whole blood by centrifugation. Pooled plasma should be obtained from a small number of donors (not more than 10) and, to ensure cross-neutralisation of the hæmagglutinins, these should be derived in fixed proportions from the different blood groups. The plasma pool must be sterile. In the preparation of citrated liquid plasma unstable proteins such as fibrinogen are removed by absorption with kaolin, and the final product contains only the stable albumins and globulins with a protein content of 4.5 per cent. It keeps for up to 2 years. Dried Human Plasma is prepared by freeze-drying the plasma pool without further treatment; care is taken during this process to ensure that the proteins are not denatured. The final product is stored in sterile sealed containers in an atmosphere of nitrogen. On reconstitution with the original volume of water it is readily soluble, and yields a solution containing 4.5 per cent protein. It must be used immediately after reconstitution. Dried plasma contains the albumins and globulins of the original blood and significant amounts of fibrinogen are preserved in it. It may be stored for up to 5 years. With either of these products the risk of transmission of infective hepatitis is very low.

In the preparation of these plasmas the labile components of the coagulation system are destroyed. For the treatment of certain hæmorrhagic states, notably hæmophilia, these components are essential, and they may be obtained from *fresh frozen plasma*. This is separated as soon as the blood has been taken, and it is immediately frozen at  $-20^{\circ}$  C. at which temperature it is stored. Gentle thawing is carried out immediately before use. The use of

fresh frozen plasma is restricted to the treatment of a few hæmorrhagic states.

*Plasma Fractions.* By chemical fractionation carried out under closely controlled conditions it is possible to separate a number of therapeutically useful plasma fractions. Gamma globulin fractions containing the antibodies may be separated; they are used as *Human Gamma Globulin Injection* in the prevention or attenuation of some of the infectious diseases (p. 520). *Fibrinogen* is prepared as a white sterile powder which is constituted with normal saline; it is used in the treatment of afibrinogenæmia and may be infused in double or quadruple strength in order to restore blood fibrinogen levels as quickly as possible. Prothrombin can readily be separated from fresh plasma. It is then converted into *thrombin* by the action of a tissue thromboplastin and calcium ions. The resulting solution is converted into a powder by freeze-drying. Human Fibrinogen clotted by Human Thrombin is used as an adhesive in plastic surgery, and in the suture of peripheral nerves. Sterile fibrinogen solutions can readily be foamed, and when this foam is clotted by thrombin and freeze-dried a fine white insoluble sponge of *Human Fibrin Foam* is formed. This is stored under sterile conditions and is used as an absorbable hæmostatic packing.

Thrombin prepared from bovine sources is also available, and may be used topically as a hæmostatic, for example in bleeding tooth sockets. Thrombin solutions must never be injected intravascularly, for they produce massive intravascular precipitation of fibrinogen with severe shock and a marked bleeding tendency.

#### PLASMA SUBSTITUTES

It has been recognised for many years that the restoration of circulatory fluid volume is life-saving in oligæmic shock; restoration of the *blood volume* is more important than replacement of lost red cells. The ideal fluid would be one with the following characteristics: an osmotic pressure (due to protein) equal to that of plasma, adequate persistence within the blood stream (but disposed of completely), and devoid of significant pharmacological or toxic actions. Ideally also it should be devoid of pyrogenic

action, be incapable of causing sensitisation, and be without effect on blood grouping. The only fluid which satisfies these criteria is human plasma itself, and whenever possible plasma should be used in the treatment of the oligæmic phase of shock. There are circumstances in which plasma substitutes have been tried. For example during the Second World War when demands for human plasma greatly exceeded supplies, and also when plasma (faultily prepared) transmitted the virus of infective hepatitis. These plasma substitutes proved to be more or less unsatisfactory and except in a major emergency they should not be given.

The most frequently used substitute for plasma is a solution in normal saline of *dextrans* of average molecular weight 75,000. The dextrans are produced from glucose by polymerisation by the organism *Leuconostoc mesenterioides*; they are then chemically degraded and purified to be approximately similar in molecular weight. Dextrans of high molecular weight persist for too long in the blood; those of lower molecular weight disappear too rapidly from the circulation. Sterilisation of dextrans is readily carried out, either by filtration or in the autoclave. Their osmotic pressure is the same as that of plasma; their persistence in the blood stream is adequate; and the effective life of the infusion is approximately 24 hours. The smaller molecules escape rapidly in the urine, producing a 50 per cent loss at 24 hours. The larger molecules remain within the blood stream, and are slowly oxidised over a period of a few weeks. Some of the dextrans are deposited within the reticulo-endothelial system. Dextrans have a number of disadvantages. They tend to cause increased rouleaux formation and so make blood-grouping difficult (a sample should therefore be taken before dextrans are transfused). If given in small doses by subcutaneous injection they are very potent antigens, but when given in massive doses intravenously they rarely elicit an antibody response. Sensitisation reactions occur in up to 10 per cent, and those who are initially sensitive remain so. It is thought that sensitivity is acquired from dextrans present in the food or synthesised in the intestine. In addition infusion of dextrans not infrequently produces a hæmorrhagic diathesis characterised by a prolongation of the bleeding time. Despite

these disadvantages dextrans are the best plasma substitute available, though clearly much inferior to plasma itself.

*Polyvinylpyrrolidone* has also been used as a plasma substitute—particularly in Germany during the Second World War. It is a synthetic water-soluble polymer of molecular weight 33,000 to 56,000. It is used in a 4 per cent solution. There are no reports that it produces sensitisation. It has the capacity to “bind” drugs, such as penicillin and insulin; it has a marked tendency to cause rouleaux formation and this in turn makes blood grouping very difficult, and raises the sedimentation rate during the 24 hours following administration. Much of the polyvinylpyrrolidone is rapidly excreted, 50-75 per cent of the dose administered being recoverable from the urine in 3 days. About 10 per cent is excreted in the bile. The remainder (fractions of higher molecular weight) is not metabolised and is apparently stored indefinitely—much of it in skin and skeletal muscle, and the remainder in the reticulo-endothelial system. Polyvinylpyrrolidone has been demonstrated in the Küpferr cells of the liver many months after its administration. This storage is apparently without adverse effect in man, though in the rat it causes reticulum cell sarcoma. For this reason—though no harmful effects have been reported in man—polyvinylpyrrolidone is now rarely used therapeutically.

Other substitutes for plasma have been tried but have not been found satisfactory. For example *acacia* is taken up from the blood stream by the liver and is stored there indefinitely; and the intravenous injection of *gelatin* involves the risk of infecting patients with tetanus, as it is difficult to ensure complete sterilisation of gelatin without denaturing the protein.



## CHAPTER 4

# ANTICOAGULANT DRUGS

INTRODUCTION. Although the mechanisms of hæmostasis seem to be well understood and the defects of the normal processes of blood coagulation causing the hæmorrhagic states have been defined, the processes associated with a tendency to intravascular thrombosis remain obscure. Yet several important diseases are characterised by this untoward event. It is probable that an increased tendency to intravascular coagulation is not the fundamental defect, and that coagulation of the blood is but one stage in a long series of events. Nevertheless, this phenomenon is almost invariably associated with clinical manifestations, and it often causes irreversible damage to the tissues rendered ischæmic. Whether an increased tendency to coagulation is present or not, it is possible to control some of the manifestations of these diseases by reducing the power of the blood to clot. This is the action of the anticoagulants

There are several methods whereby blood may be rendered incoagulable. Some of these —such as mechanical defibrination — are clearly not applicable to the treatment of patients. Removal of ionised calcium as an insoluble salt by oxalate, citrate and chelating agents is an effective method of preventing coagulation; but these procedures cause severe tetany and distress long before any anticoagulant action is noted. The therapeutically useful anticoagulants fall into two categories; (i) *heparin* and like substances which have a strong anticoagulant action both *in vivo* and *in vitro*; and (ii) the “coumarin” group of anticoagulants which have no *in vitro* effect on clotting, but when administered to the intact animal interfere with the mechanism of coagulation.

Anticoagulant therapy is now well established as part of the management of most patients who develop coronary artery thrombosis. It is also invaluable in post-operative venous thrombosis and pulmonary embolism, and it has some place in the treatment of thrombophlebitis. The anticoagulants are used

## ANTICOAGULANT DRUGS

routinely in the practice of vascular surgery. Details are to be found in textbooks of therapeutics and in special monographs.

### HEPARIN

Heparin is obtained from the liver and lungs of animals by a process of extraction. The extracts are sterilised either by autoclaving or filtration, and the content of heparin is standardised after laboratory testing of activity. The exact chemical composition of heparin is not known, but it is a mixture of dextrorotatory mucopolysaccharide esters of sulphuric acid—mucoitin polysulphuric acid. In the standard preparations this is present as a sodium salt. The average molecular weight is about 20,000. Heparin is probably not a single pure chemical, but a mixture of very similar substances with similar biological properties. By virtue of its chemical composition the molecule of heparin carries a strong electro-negative charge, and it is this charge which produces the anticoagulant effect.

Heparin is one of the physiological anticoagulants. Its precursors are present in many tissues of the body (especially those rich in mast cells) and in particular the liver and lung from which it is commercially extracted. Heparin precursors in the mast cells produce the characteristic metachromatic staining reaction. When admixed with whole blood heparin has several different modes of action: platelet disintegration is slowed; the conversion of prothrombin to thrombin by the action of thromboplastin is prevented; and the action of thrombin in converting fibrinogen to fibrin is also inhibited. There are no chemically active groups in heparin; and it is the strong electrical charge which inhibits these enzymatic reactions; the effect is exerted on whole blood rather than on any of the specific components of the coagulation system.

In normal dosage and perhaps also physiologically heparin has one other striking action: in the intact animal alimentary lipæmia is cleared. Synthetic heparin-like substances also have this action, and it is lost if the charge on the molecule is removed. The reduction of lipæmia is accompanied by the passage of fat from the circulating blood into the tissues. The implications of this action of heparin are not understood, and it is not at the moment of therapeutic importance. No other actions of heparin are known.

When used as a drug it is the physiological anticoagulant action of heparin that is employed. The dose given is adjusted according to the effect on the clotting time of the whole blood, and this is maintained at 15-20 minutes (method of Lee and White: normal 5-7 minutes). Toxic effects are rarely encountered. Sensitisation reactions may occur, usually in patients with an allergic diathesis; asthma, urticaria or an anaphylactoid reaction can be produced, but these side-effects are rare. Alopecia has occasionally been reported. Heparin has no action on extravascular fibrin, and therefore wound healing is not significantly upset. Hæmorrhage should be regarded as a sign of overdosage: it is not strictly a toxic effect. If bleeding from overdose occurs two substances with strongly positive charges may be used to neutralise the heparin effect. Protamine Sulphate Injection (a 0.5 per cent solution) by slow intravenous injection weight for weight (in mg.) of heparin to a maximum of 50 mg. gives an immediate action which lasts for about two hours. Toluidine blue in a dose of 4-6 mg./Kg. by slow intravenous injection gradually takes effect, but its action lasts for many hours.

Heparin is ineffective when given by mouth, and though readily absorbed from subcutaneous and intramuscular injection sites it is best given *intravenously* for therapeutic purposes. It is bound to plasma protein and circulates within the intravascular compartment, but blood levels fall quickly and it has a short duration of action. A small fraction is excreted in an active form in the urine and a rather larger fraction in an inactive form; the rest seems to be destroyed in the body—probably by heparinases in the liver. After the administration of antidotes to heparin all the heparin is destroyed in the tissues.

The action of heparin begins within ten minutes of its intravenous injection, and the intensity and duration of action are roughly proportional to the dose. After the heparin action wears off there is no rebound phase of increased coagulability. The intravenous preparation is a sterile solution of the sodium salt, usually containing 5,000 International Units (equivalent approximately to 50 mg.) in each ml.; concentrations up to 25,000 Units per ml. are prepared. In the dry state it keeps indefinitely. A dose of 10,000 Units intravenously usually produces adequate pro-

## ANTICOAGULANT DRUGS

longation of the clotting time for 4-6 hours; a further dose is then required. A fixed dose scheme should not be used, but enough heparin should be given to obtain the required prolongation of the clotting time. The daily total dose should not exceed 30,000 Units. Larger doses of more concentrated preparations may be given by intramuscular injection every twelve hours, say 25,000 Units. This may give an adequate anticoagulant action, but it is not fully reliable. A depot preparation in Pitkin's menstruum is available for intramuscular injection, and this may be employed in maintenance therapy to spare the patient repeated vein puncture. It is less reliable and higher doses have to be used, though the effect is more prolonged. Intramuscular injection of heparin often causes local pain, and hæmatoma formation may be troublesome.

In practice therapy with heparin is rarely prolonged. It is employed for its rapid action which gives an immediate anticoagulant effect. This is used for approximately 48 hours by the end of which time the orally effective coumarin group anticoagulants will have achieved a significant interference with blood clotting. Heparin is then discontinued. However, some surgeons (especially specialists in cardiovascular diseases) use heparin for the duration of anticoagulant therapy. There seems to be no clear evidence however that it is a "better" anticoagulant, though its use represents a more physiological approach to therapy.

## DEXTRAN SULPHATE

Dextrans of molecular weight 7,000 8,000, when sulphated, have a strong electro-negative charge, and have an anticoagulant action and a lipæmia-clearing effect apparently identical with that of heparin. The potency is much less than that of heparin, but the duration of action is twice that of heparin, so that a dose of 330 mg. twice daily may be adequate for therapeutic purposes. It is cheaper than heparin and can be chemically purified and standardised. Sensitisation reactions have been described, but as the molecular weight of dextran sulphate is relatively low, these effects are rare. In the control of therapy the methods applicable to heparin treatment are adopted. It should be noted, however, that when overdosage with dextran sulphate

occurs, protamine sulphate sometimes proves to be an unreliable antidote. Although Dextran Sulphate Injection is an important and potentially valuable preparation it has not yet been used on a sufficiently large scale to permit of an adequate assessment of its place in clinical practice.

### THE COUMARIN GROUP

In the winter of 1921-2 a new hæmorrhagic disease was reported in cattle in Alberta; it occurred only in the animals that had eaten spoiled sweet clover. It was immediately suspected that the bleeding was attributable to a toxic substance in the clover, but it was not until 1941 that the toxic agent was isolated and identified. It was methylenedihydroxycoumarin (Dicoumarol) which had been synthesised as early as 1903. This was the first orally active anticoagulant, and many coumarin derivatives with more useful properties have subsequently been synthesised; the original substance is no longer used. All the members of this group and certain other orally acting anticoagulants, the indanediones, have an identical action, and they are loosely referred to as the "coumarin group". The most commonly used member of this group, though chemically not a coumarin, is phenylindanedione or phenindione; this is the only member of the group which will be discussed in detail.

### PHENINDIONE

This synthetic indanedione derivative possesses anticoagulant activity of the coumarin type; that is to say its action is due to interference with the hepatic synthesis of thromboplastin components—in particular prothrombin and factor VII. This action is one of *Vitamin K antagonism* and can be reversed by giving an excess of Vitamin K. When prothrombin and factor VII become depleted in the peripheral blood thromboplastin formation is impaired and so blood coagulability is reduced. This state of reduced coagulability persists as long as treatment is continued. Before its onset there is a latent period. This arises from a combination of two factors: (i) the slow removal from the blood of the prothrombin and factor VII present before the start of therapy; and (ii) the rate of action of the anticoagulant on the

liver. When therapy is stopped the reverse of this process is seen: there is some delay before normal levels are regained—the result of continuing action of the drug, and the slow restoration of the prothrombin and factor VII to normal. With phenindione a therapeutic effect is usually obtained between 48 and 72 hours after the first dose. On cessation of therapy the prothrombin time does not rise for 24 hours, but returns to normal by 48 to 60 hours.

When ordinary glass test tubes are used the coumarin group of anticoagulants have no effect on the clotting time, though anticoagulant action may be so intense that it causes hæmorrhage. Some prolongation of the clotting time can be demonstrated if siliconed glassware is used, but this is not a satisfactory basis for controlling therapy. Another index, Quick's "One Stage Prothrombin Time", is used. Citrated plasma is mixed with an excess of an extrinsic thromboplastin and then recalcified. The speed at which coagulation takes place was initially thought to reflect the concentration of prothrombin, but is now known to depend on the concentration of at least three factors—prothrombin, factor V and factor VII. Despite its misleading implication the term "Prothrombin Time" is convenient and has been retained. Phenindione depresses hepatic synthesis of both prothrombin and factor VII and so prolongs the prothrombin time, which forms a convenient method of control of anticoagulant action. As the components of the coagulation system are present in a quantity in excess of what is required for coagulation, significant impairment of clotting is not obtained until the prothrombin time is increased to at least twice that of a normal (control) plasma. Should the levels be further depressed so that the prothrombin time exceeds more than three times the control, spontaneous hæmorrhage is likely. Until these levels are reached the only demonstrable defect of hæmostasis is in thromboplastin production, but at very low levels of prothrombin activity vascular fragility is much increased.

In anticoagulant therapy the prothrombin time should be maintained at about two and a half times the control value. Prothrombin times which are less than twice those of the control are not associated with significant anticoagulant action; if the prothrombin time is more than three times that of the control,

hæmorrhage is likely to occur. The predictability with which the therapeutic level can be maintained with a given dose of anticoagulant varies for each member of the coumarin group; phenindione gives a relatively predictable and smooth control.

The need for the determination of the prothrombin time is one of the disadvantages of the coumarin group of anticoagulants. A venepuncture and the facilities of a laboratory are required. In the early stages of treatment the prothrombin time should be estimated daily, but later—particularly with effects as predictable as those of phenindione—when the response to anticoagulants has been determined, a weekly or even fortnightly estimation may suffice. With some of the other members of the group, though the dose may be constant, considerable fluctuations in prothrombin time are found and the level must be estimated not less than twice a week.

The main toxic effect of phenindione is in fact the result of overdose which readily occurs if estimation of the prothrombin time is not performed frequently enough. The commonest complication is hæmorrhage—usually from bowel or bladder. If the prothrombin time is adequately checked, the predictability of phenindione is such that hæmorrhage should not occur. Sensitisation reactions are seen infrequently; a skin rash may be found, or hæmatological signs of sensitisation may appear. Reports of toxic effects on the liver and kidneys have not been confirmed, though the action of phenindione is much prolonged in the presence of advanced renal or hepatic disease. Salicylates also potentiate the action of phenindione, but neither should cause trouble if the prothrombin time is estimated sufficiently frequently. Phenindione produces a pink colour in the urine; this should not be mistaken for hæmorrhage.

Phenindione is well absorbed by mouth. It exerts its action in the liver. The further metabolism is not known, but the increased effect when there is hepatic and renal disease suggest that these viscera must be the sites of detoxication and excretion. It is supplied in tablets for oral administration and the initial daily dose is 100–200 mg. Thereafter the dose should be regulated according to the prothrombin time, the maintenance dose usually being about 50–75 mg. daily. This may be given as a single dose.

## ANTICOAGULANT DRUGS

It is common practice when using coumarin-like anticoagulants to administer heparin to obtain anticoagulant action during the preliminary phase—between the administration of the oral anticoagulant and the onset of its full effect.

The antidote to hæmorrhage produced by overdose with phenindione is Vitamin K<sub>1</sub> which is given as an intravenous injection of an emulsion of the oxide. Within four hours the prothrombin time should be restored to nearly normal. Should a more rapid effect be required, fresh blood or fresh frozen plasma may be used. Water-soluble Vitamin K analogues do not antagonise the action of the coumarin group of anticoagulants.

### OTHER ANTICOAGULANTS OF THE COUMARIN GROUP

These differ in the speed of onset of action, the duration of effect, and the ease with which continuous control may be attained. Ethylbiscoumacetate was one of the early and more satisfactory coumarin derivatives; it is still used, but it is not entirely satisfactory in that control of the action is difficult and frequent estimations of prothrombin time are necessary. As its action is of short duration the daily dose of ethylbiscoumacetate must be divided into at least two portions. Onset and disappearance of action are rapid. Ethylbiscoumacetate differs from all the other members of the coumarin group in that it causes a selective depression in the production of factor VII.

*Cyclocoumarol* has a very prolonged action and is of value for long-term anticoagulant therapy, though variations in sensitivity may cause trouble. The action of *Warfarin sodium* is very similar to that of phenindione and this preparation seems—after limited trial—to be equally satisfactory, though it offers no advantages. Dicoumarol is slow in action and difficult to control, and is no longer used.



## CHAPTER 5

### VITAMINS

INTRODUCTION. The student who is well grounded in the physiology of the *vitamins* has little or nothing to learn from pharmacologists on this subject; and as clinical experience allows him to recognise maladies which are proved to be deficiency states, the student's knowledge of physiology is assimilated into therapeutics. In some parts of the world the avitaminoses, occurring as merely one manifestation of malnutrition, poverty and ignorance, are among the commonest disorders seen by the doctor; on the other hand there are countries in which a high standard of living has virtually eliminated the diseases caused by avitaminosis.

The dietetic needs of the healthy man are fully discussed in standard works on physiology and biochemistry. In brief he requires the "proximate principles" (protein, fat and carbohydrate), mineral salts and water; and he must have appropriate quantities of vitamins originally called "accessory food factors". Dietetic habits appear to vary considerably even among members of the same community living under comparable conditions. In general, however, the "balance" between the various food constituents is maintained by taking a generous mixed diet; and in these circumstances the vitamin content of the food is satisfactory under ordinary conditions. There are times, however, when a state of "relative deficiency" or "conditioned deficiency" may be created. For example, metabolic requirements may increase rapidly in the growing child and in the pregnant woman; there may be failure of absorption as in ulcerative colitis or in the malabsorption syndrome; or utilisation may be "blocked", as occurs during anticoagulant therapy with the coumarin group of compounds.

Occasionally even in countries where malnutrition is uncommon the diet may be grossly deficient in one or more of the vitamins. There are usually obvious factors responsible for this; for example, the elderly person living alone on an old-age pension, the

## VITAMINS

mentally defective, or those who have restricted their diet severely for many years for therapeutic reasons. In any of the above circumstances clear evidence of vitamin deficiency in the form of specific disease syndromes such as pellagra or scurvy may arise, and may require treatment. It may also be possible to forestall the development of the deficiency syndrome when these predisposing conditions are recognised by giving prophylactic supplements of vitamins. Having made good the deficiency, attention should then be directed to maintaining the progress of the patient by sensible advice on his diet. Vitamins are *not* "tonics". They should never be prescribed as placebos in view of the cost involved to the patient and the community; and they should not be administered for the treatment of alleged sub-clinical deficiencies which could be easily rectified by a simple enquiry into such matters as the quantity, quality, storage and preparation of the patient's food.

The student is recommended to revise fully the physiology of vitamin action. The pharmacological interest in this subject lies (i) in the large curative doses used in the treatment of florid deficiency states, (ii) the use of vitamins as ancillary treatment in diseases other than avitaminoses - for example calciferol in lupus vulgaris, and (iii) the occasional toxic effects of overdosage. The chemistry of the vitamins is now well known, but by custom the classification used is based on the early division into two groups - "Fat-soluble A" and "Water-soluble B", and the later extension of the alphabetical designation.

## FAT-SOLUBLE VITAMINS

### VITAMIN A

This substance is made in the body from various precursors belonging to the group of naturally-occurring carotene pigments. In the absence of carotene Vitamin A cannot be synthesised.

*Sources.* Carotene is plentiful in green vegetables, a few root-plants (notably carrots) egg-yolk, milk and butter. Fish obtain carotene from sea-plants. Rich animal sources of ready-made Vitamin A are fish-liver oil, mammalian liver and in lesser

quantity, milk-fat. Margarine and milk-powders are often "fortified" with Vitamin A.

*Chemistry.* Vitamin A is a complex primary alcohol. Of the carotene pigments  $\beta$ -carotene predominates in nature, and this, on conversion, gives rise to two molecules of Vitamin A. Standardisation of Vitamin A preparations is by biological assay on the growth of vitamin-deficient rats, the present international unit being equivalent to the activity of 0.3  $\mu$ g. of Vitamin A alcohol. Vitamin A is stable to heat, but its destruction is accelerated by light or by oxidising agents.

**PHYSIOLOGICAL FUNCTIONS, AND SYMPTOMS OF DEFICIENCY.** Vitamin A is essential for the formation of visual purple in the retina, on which good night-vision depends, and it promotes the integrity of the epithelial cells of the skin, eyes, upper respiratory tract, and urinary tract. Thus gross deficiency of Vitamin A may give rise to the following clinical features—night blindness, xerophthalmia (dryness followed by keratinisation of the conjunctiva), squamous metaplasia of the mucosal surface of the upper respiratory tract, follicular hyperkeratosis of the skin ("toad-skin"), and a high susceptibility to the formation of renal calculi. In clinical practice avitaminosis A is rare as an isolated deficiency state, though some of the above features may occur as part of an advanced state of malnutrition or subnutrition—for example, in concentration camps where prisoners are accommodated under famine conditions.

*Daily Requirements.* An average adult requires 2,500–5,000 I.U. of Vitamin A daily. The requirement rises to 6,000–8,000 I.U. daily during pregnancy and lactation.

*Absorption, Fate and Excretion.* Pre-formed Vitamin A is readily absorbed by the normal bowel, but as it is fat-soluble it may be poorly absorbed if the patient is suffering from steatorrhœa. Its precursor carotene is not readily absorbed if bile is absent from the bowel, but the absorption of Vitamin A is not materially affected. Carotene is converted in the wall of the small bowel into

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Vitamin A, which is then stored in large quantity in the liver. Some carotene gains direct access to the circulation, occasionally accumulating in excessive quantities (carotinæmia). Carotene and Vitamin A are destroyed slowly in the body: even when the intake is high there is little urinary excretion.

*Toxic Effects of Overdosage.* Overdosage has been recorded in children given excessive supplements of Vitamin A. The features described include anorexia, dryness of hair and skin, and hyperostotic swellings on the long bones.

*Preparations and Dosage.* Numerous official and proprietary preparations exist. Suitable examples of the official preparations are: Halibut Liver Oil Capsules, each of which contains about 4,500 I.U. of Vitamin A, with a variable Vitamin D content; Concentrated Solution of Vitamin A, which contains 50,000 I.U. per G. (dose 0.06 to 0.6 ml.); and Vitamin A Capsules (Strong) BNF containing 50,000 I.U. per capsule (dose 1 or 2 capsules daily).

**THERAPEUTIC USES.** High dosage (up to 100,000 I.U. daily) rapidly abolishes the deficiency states. The administration of supplements of Vitamin A to expectant mothers, nursing mothers and infants is justifiable. However, it seems unlikely that Vitamin A has any useful action in the treatment or prevention of the many conditions for which it has been recommended in the past.

## VITAMIN D.

The pharmacology of Vitamin D is simply the applied physiology of the subject, and this includes the process of bone formation and calcium and phosphorus metabolism.

*Sources.* Natural Vitamin D is present in only a few foodstuffs: the liver oils of fish (notably cod and halibut) are rich sources, and smaller quantities occur in egg-yolk, summer milk and butter. Various brands of margarine and baby foods are "fortified" with Vitamin D. On exposure to ultraviolet light Vitamin D is formed in the skin from sterol precursors.

**Chemistry.** Many substances of the sterol group have been shown to exhibit Vitamin D activity, but those of prime importance are: (1) Calciferol (Vitamin D<sub>2</sub>) which is a synthetic Vitamin D, and is the most active (in terms of Vitamin D activity) of the group of substances derived from ergosterol by ultra-violet irradiation, and (2) Vitamin D<sub>3</sub> which is the natural Vitamin D found in fish-liver oil. Vitamin D<sub>3</sub> is identical with the substance formed *in vitro* from 7-dihydrocholesterol by ultra-violet irradiation; and it is synthesised in the human skin on exposure to ultra-violet light. There is an abundant supply of sterol substances in the body (e.g. cholesterol, steroid hormones), and even the light from the overcast skies of temperate zones provides sufficient irradiation to maintain supplies of Vitamin D. The international unit is equivalent to the activity of 0.025 µg. calciferol.

**PHYSIOLOGICAL FUNCTIONS, AND SYMPTOMS OF DEFICIENCY.** Many of the details of calcium metabolism are still disputed, but it is certain that Vitamin D plays an important role. The bony skeleton is composed mainly of calcium salts. In blood serum, however, available calcium circulates in the ionised state and it is essential for normal neuromuscular function. There is a critical point at which reduction of the ionised calcium invokes a compensatory mechanism, the secretion of parathyroid hormone - which mobilises bone calcium. Further, Vitamin D in physiological quantities permits the uptake of replacement calcium from the intestine. The rising extracellular concentration of calcium then depresses parathyroid activity.

In the absence of Vitamin D hypersecretion of parathyroid hormone continues with demineralisation of the skeleton. Paradoxically, a gross excess of Vitamin D also produces a parathyroid-like effect, with mobilisation of skeletal calcium, probably as a result of an increase in the excretion of phosphate in the urine. A closely related substance (Dihydrotachysterol) has marked parathyroid-like activity, without exhibiting antirachitic properties. It is separately discussed below.

Deficiency of Vitamin D *during the period of skeletal growth* may lead to the clinical condition called rickets in which defective bone

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formation progresses to gross deformities. The nature of the deformities is determined by the physical stresses to which the skeleton is subjected: standing and walking tend to cause bowing of the legs. In this disease also the low level of ionised serum calcium may precipitate neuromuscular dysfunction (convulsions, carpopedal spasm and laryngismus stridulus). The deficiency may be partly of dietary Vitamin D, but there are often associated factors of great importance— inadequate exposure to ultra-violet irradiation (a common occurrence in smoky industrial towns and cities) and a dietary deficiency of calcium in a form suitable for rapid assimilation. Until recent years up to 85 per cent of children were affected in varying degrees in some industrial districts. Rickets however is now a rare disease—thanks to adequate ante-natal care, closer attention to the needs of infants and school children, the provision of vitamin supplements and cheap milk for expectant mothers, nursing mothers and infants, and a growing awareness of the value of exposure to fresh air and sunlight.

The allied condition osteomalacia occurs *in adults*, usually in malabsorption states or as a result of gross and prolonged dietary deficiency.

*Daily Requirements.* The adult daily requirement of Vitamin D is small, and supplementary intake does not reduce the requirement of dietary calcium. The infant and young child require about 400 I.U. daily, and it is wise to provide a similar intake for women during pregnancy and lactation.

*Toxic Effects of Overdosage.* A grossly excessive intake of Vitamin D is not uncommon. Many children receive supplements in various forms without adequate supervision. An early feeling of well-being is replaced by loss of appetite, nausea, headache, sweating and diarrhoea. Urinary and blood calcium levels rise, and this creates the danger of metastatic calcification in the heart, blood vessels, and renal parenchyma. Polyuria and renal failure may ensue, but in the early stages the changes are reversible.

*Absorption, Fate and Excretion.* Vitamin D is fat-soluble and its absorption from the alimentary tract is dependant on the presence

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of bile. Absorption is greatest if the doses are spread over the day, hence the especial value of, say, "fortified" infant foods. Storage in the body is limited, but excretion is also very slow; some excretion occurs in the milk during lactation. •

*Preparations.* Numerous official and proprietary preparations exist, but the following are usually suitable for therapeutic use: Calciferol Tablets, each of which contains 1.25 mg. calciferol (50,000 I.U. of Vitamin D activity); Calcium with Vitamin D Tablets, each of which contains calcium sodium lactate, calcium phosphate and calciferol equivalent to 500 I.U. Vitamin D activity. "Cod Liver Oil Compound" as supplied by Welfare Departments of local authorities contains 700-800 I.U. per teaspoonful dose.

**THERAPEUTIC USES AND DOSAGE.** In infant feeding, and for nursing or expectant mothers, a daily supplement of 500 I.U. in one or other of the above forms is recommended.

The treatment of established rickets requires a larger dose: 3,000-5,000 I.U. daily is recommended and much larger dosage is sometimes given. Other factors, especially the provision of adequate quantities of milk, vegetables, eggs and butter are also highly important.

Vitamin D or its analogues (see below) may be used in the long-term control of hypocalcæmic tetany, after initial correction of the low serum calcium by giving a suitable preparation intravenously—for example calcium gluconate. A temporary increase in the serum calcium levels can also be achieved indirectly by giving parathyroid hormone, but in practice this is rarely used.

Osteomalacia in adults is treated by administration of Vitamin D, and by ensuring an adequate dietary intake of calcium.

Lupus vulgaris has been treated successfully by the administration of high dosage of Vitamin D—quantities which produce toxic effects. The mechanism of this action is uncertain.

## DIHYDROTACHYSTEROL

This substance deserves mention. It is often known by its proprietary name "A.T.10", and is another in the series of compounds produced by the irradiation of ergosterol.

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**ACTIONS.** Dihydrotachysterol has a much smaller influence than Vitamin D on calcium absorption from the intestine, but by increasing the renal excretion of phosphate it mobilises skeletal calcium, thus producing a similar effect to natural parathyroid hormone. The value of dihydrotachysterol in therapeutics is therefore primarily in the treatment of hypoparathyroidism.

**Toxic Effects.** The effects of overdosage are similar to those produced by hypervitaminosis D—nausea, polyuria, thirst and metastatic calcification.

**Absorption, Fate and Excretion.** Dihydrotachysterol is effectively absorbed when given orally, and this is an advantage over preparations of parathyroid hormone. It is slowly destroyed in the body.

**Preparations.** "A.T.10." This is an oily preparation containing 1.25 mg. dihydrotachysterol per ml. For the treatment of hypoparathyroidism an initial dose of 3 ml. is recommended; the maintenance dose is thereafter adjusted according to clinical progress, serum and urinary calcium output, and is usually about 0.5–1 ml. daily. In addition, a high-calcium low-phosphate diet is taken, and aluminium hydroxide administered to reduce phosphate absorption. It is possible to use large doses (40,000–50,000 I.U. daily) of calciferol as an alternative to dihydrotachysterol in this condition.

## VITAMIN K

Substances of the Vitamin K group are required for the formation of prothrombin, a substance which takes part in the normal blood-clotting mechanism.

**Sources.** Natural sources include alfalfa, fish meal, casein, green vegetables and many vegetable oils. Animal faeces are rich in Vitamin K, because it is synthesised by the normal bacterial flora of the intestine: this is thought to be the source of the major part of human Vitamin K requirement.



*Chemistry.* The compounds exhibiting Vitamin K activity are derivatives of naphthaquinone. Naturally occurring examples are Vitamin K<sub>1</sub> and Vitamin K<sub>2</sub>; synthetic analogues include menaphthone. Natural Vitamin K is a fat-soluble oil, menaphthone is a fat-soluble crystalline powder, and certain complex salts of menaphthone are water-soluble.

PHYSIOLOGICAL FUNCTIONS, AND SYMPTOMS OF DEFICIENCY. The method by which Vitamin K regulates prothrombin formation is uncertain. It is presumed that an enzyme reaction in the liver cell is dependent on the presence of Vitamin K.

The exact requirement is unknown: in health the needs of the body are met from the diet and by bacterial synthesis in the intestine.

Deficiency of Vitamin K leads to a hæmorrhagic state due to insufficiency of prothrombin. The deficiency is expressed in terms of the "prothrombin time"—the prothrombin time being compared with that of a normal person. This may be seen in the neonatal period (until normal bacterial flora is established in the infant's bowel), in obstructive jaundice or steatorrhœa, or during administration of drugs which "block" the formation of prothrombin, i.e., coumarin group. No other pharmacological actions of Vitamin K are recorded, nor do toxic effects occur in man from therapeutic doses.

*Absorption, Fate and Excretion.* Natural Vitamin K<sub>1</sub> and Vitamin K<sub>2</sub> and also menaphthone are well absorbed only in the presence of bile salts. The sodium bisulphite and sodium diphosphate salts of menaphthone, however, are water-soluble and may be well absorbed even in obstructive jaundice. Both water-soluble and oily forms are well absorbed if they are injected intramuscularly.

*Preparations and Dosage.* Official preparations are Acetomenaphthone Tablets, each of which contains acetomenaphthone 5 mg. (dose 5–10 mg.), and Menaphthone Injection, which contains 5 mg. in each ml., in oily solution. Vitamin K<sub>1</sub> is usually given in the form of Phytonadione, USP, by injection (see p. 672).

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**THERAPEUTIC USES.** The main therapeutic uses of Vitamin K and its analogues are in the prevention of neonatal hæmorrhage by administration to the mother at the onset of labour; in the pre-operative management of jaundiced patients; and in the correction of drug-induced hypoprothrombinæmia. (p. 87). Vitamin K is of no value in other hæmorrhagic states.

## VITAMIN E

Despite extensive investigation there is as yet no convincing evidence to show that substances of the Vitamin E group have any place in the practice of therapeutics in man.

*Sources.* Wheat-germ oil, cotton-seed oil and egg-yolk contain Vitamin E.

*Chemistry.* Vitamin E activity is shown by the substances in the tocopherol group (*alpha*, *beta*, *gamma* and *delta* tocopherol): their outstanding chemical property is the antagonisation of oxidation processes. They are yellow oils, which can be crystallised and are then fat-soluble.

**PHYSIOLOGICAL FUNCTIONS.** It appears that in laboratory animals the absence of tocopherol causes certain tissues to undergo degenerative changes: deficiency states include testicular degeneration, habitual abortion, muscular dystrophy or necrotising arteritis with associated myocardial degeneration and cardiac failure. There is no evidence that deficiency in man leads to any of these conditions.

One international unit is equivalent to 1 mg.  $\alpha$ -tocopherol acetate. No other pharmacological actions are recorded, and tocopherol has no toxic effects.

*Absorption, Fate and Excretion.* Absorption from the bowel is incomplete, but there is adequate storage of tocopherol in adipose tissue.

*Preparations.* Tocopherol Acetate is prescribed in a dose of 3–10 mg. Though this substance has been used widely in the treatment

of habitual abortion, male infertility, muscular dystrophy, cardiovascular and other diseases, its therapeutic value has not been established.

## WATER-SOLUBLE VITAMINS

### THE VITAMIN B COMPLEX

Many members of this group have now been identified. Although they differ widely in chemical structure, they are best considered as a group: their natural sources are the same; their physiological functions have much in common; and deficiency diseases can rarely be correlated exclusively to lack of one component of the B group of vitamins. The Vitamin B complex is conveniently subdivided as follows:

Group 1.	Cyanocobalamin	}	Essential to normoblastic erythropoiesis (see p. 70).
	Folic Acid		
2.	Aneurine	}	Of proven "Vitamin" nature in man and of value in therapeutics.
	Nicotinamide		
	Riboflavine		
3.	Pyridoxine	}	Of doubtful "Vitamin" nature in man, and not proved to be of therapeutic value.
	Pantothenic Acid		
	Biotin		
4.	Choline	}	Regarded as essential nutrients rather than vitamins.
	Inositol		
	<i>p</i> -Aminobenzoic acid		

In medical practice in Western Europe deficiencies of these vitamins are usually secondary to (or "conditioned" by) gastrointestinal disease and hyperemesis, and occasionally by neglect and low intelligence; the deficiency therefore tends to include all members of the Vitamin B complex, and the best prophylactic or therapeutic results are obtained by the administration of preparations containing all the important factors, preferably in a natural form, e.g. yeast or yeast concentrates.

*Aneurine.* (Vitamin B<sub>1</sub>, Thiamin)

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*Sources.* Yeast, cereal husks, liver and egg-yolk are natural sources of aneurine. It has been suggested that aneurine may be synthesised in the human intestine, but proof of this is lacking.

*Chemistry.* Aneurine is a molecule of complex structure: it contains pyrimidine and thiazole rings. It is available in pure crystalline form and is easily synthesised. Aneurine is water soluble.

**PHYSIOLOGICAL FUNCTIONS: SYMPTOMS OF DEFICIENCY.** The phosphorylated form of aneurine is the precursor of the enzyme carboxylase and this plays an important role in the cycle of carbohydrate metabolism: deficiency of aneurine results in an accumulation of lactic and pyruvic acids in the circulation. These metabolites promote vasodilatation, "high output" cardiac failure and gross œdema—a syndrome known as beri-beri. The state of œdema (dropsy) may be aggravated by deficiency of plasma protein—a result of chronic malnutrition—with a corresponding failure of the plasma to hold water in circulation. Nutritional polyneuropathy is related, though less constantly, to aneurine deficiency; and in Britain Wernicke's encephalopathy is seen in the conditioned deficiencies referred to above. These diseases are less clear-cut than was originally suggested: multiple vitamin deficiency and gross malnutrition often contribute to the full clinical picture. Deficiency states tend to arise more rapidly if the intake of carbohydrates is disproportionately high, e.g. beri-beri is classically a disease of the East—where the diet may consist almost entirely of rice—the polished rice from which vitamin-containing husk has been removed.

*Daily Requirement.* This is estimated at 1–2 mg. Biological assay is unnecessary as the pure crystalline product is available. Other pharmacological actions are not important, though slight vasodilatation with a fall in blood pressure may follow administration.

*Absorption, Fate and Excretion.* Aneurine is freely absorbed on intramuscular injection, but it is incompletely absorbed from the

bowel. The vitamin is distributed to all tissues, especially to the liver. About 1 mg. per day is completely broken down in the tissues. If large amounts of aneurine are taken, the excess over requirements is excreted rapidly in the urine.

*Preparations and Dosage.* Suitable preparations include Aneurine Hydrochloride Injection, which contains aneurine hydrochloride 25 mg. per ml.; a dose of 20-50 mg. is given by subcutaneous or intramuscular injection. Aneurine Hydrochloride Tablets are available in strengths of 3 mg., 10 mg., 25 mg. and 50 mg.; a therapeutic dose of 20-50 mg. daily is given.

**THERAPEUTIC USES.** Aneurine in the above dosage rapidly corrects deficiency of the vitamin in the tissues. Faults in the dietetic regimen and in general hygiene should receive appropriate attention. Aneurine does not influence those forms of neuritis, cardiovascular degeneration, or mental disturbance which are not attributable to deficiency of this vitamin.

#### NICOTINIC ACID AND NICOTINAMIDE (Pellagra-preventing, or P.P. factor)

*Sources.* Nicotinic acid and its amide are distributed widely in nature: liver, yeast, milk, cheese and cereals are rich sources. Tryptophan is the precursor for the synthesis of nicotinamide in the intestine and the tissues.

*Chemistry.* The molecule of nicotinic acid is a simple organic acid, pyridine  $\beta$ -carboxylic acid. The acid and its amide are white, crystalline, water-soluble and heat resistant.

**PHYSIOLOGICAL FUNCTIONS, AND SYMPTOMS OF DEFICIENCY.** Nicotinamide is a constituent of co-enzymes I and II. It takes part in many oxidation reactions in the body, and is indispensable to normal protein metabolism. Deficiency occurs classically in maize-eaters, producing *pellagra*, but "conditioned" pellagra-states may occur in alcoholism, gastro-intestinal disease and mental disturbances. The clinical manifestations of this disease include pigmentation of the skin, especially those parts

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which are exposed to sunlight and also the pressure points and where there is chafing; there are gastro-intestinal upsets including diarrhoea and a characteristic appearance of the tongue; and mental deterioration is common. Other possible factors which contribute to the onset of pellagra are discussed in textbooks of medicine.

*Daily Requirement.* This is estimated to be 10-12 mg.

*Other Pharmacological Actions.* Nicotinamide exhibits no other actions worthy of note, but nicotinic acid is a potent vasodilator, especially of the capillary bed. Though there is a close chemical relationship between these substances and nicotine, they show none of the potent pharmacological actions of the alkaloid.

*Absorption, Fate and Excretion.* Nicotinamide is absorbed from the intestine, and stored in the liver. Excretion is by the kidney in the N-methylated form.

*Preparations and Dosage.* Nicotinamide Injection contains 50 mg. per ml.; the therapeutic dose is 50-250 mg. Nicotinamide Tablets contain 50 mg. each. The prophylactic dose is 15-30 mg. daily and the therapeutic dose is 50-250 mg. daily. Nicotinic Acid Tablets contain 50 mg. each and the therapeutic dose is 50-250 mg. daily.

**THERAPEUTIC USES.** To avoid the unpleasant side-effects of nicotinic acid, nicotinamide is preferred in the treatment of pellagra and in prophylactic use in the dosage indicated. If it is desirable to promote vasodilatation, for example in Raynaud's disease, nicotinic acid may be used.

## RIBOFLAVINE

*Sources.* Riboflavin (Lactoflavin) occurs with the other vitamins of the B group in yeast, milk, liver, egg-yolk and also in vegetable leaves. Bacterial synthesis occurs in the human gut.

*Chemistry.* Pure riboflavin consists of orange-coloured crystals. Chemically it is 6:7-Dimethyl 9(*D*-1-ribityl)isoalloxazine.

**PHYSIOLOGICAL FUNCTIONS, AND SYMPTOMS OF DEFICIENCY.** The phosphorylated derivative is a component of several flavoproteins which are concerned with the transport of hydrogen in oxidative enzyme reactions. Deficiency is believed to lead to angular stomatitis, cheilosis (a loss of epithelium at the mucocutaneous junction of the lips), a peculiar magenta pigmentation of the tongue, and sometimes vascularisation of the cornea (though the last sign is of doubtful aetiology).

*Daily Requirement.* This is estimated at 1 mg. daily. No biological assay is necessary as the pure substance is available.

*Absorption, Fate and Excretion.* Riboflavine is readily absorbed from the intestine and by injection. It is distributed to all tissues but is poorly stored. Any excess over requirements is excreted unchanged in the urine.

*Preparations and Dosage.* Riboflavine Tablets are available in 1 mg. and 3 mg. strengths. The prophylactic dose is 1-4 mg. daily and the therapeutic dose is 5-10 mg. daily.

**THERAPEUTIC USES.** Therapeutically, riboflavine is of course used when ariboflavinosis has been diagnosed, but the syndrome—as an isolated clinical condition—is rare. The vitamin is much more frequently used—along with others—as a safeguard in illnesses which are likely to be complicated by multiple avitaminoses. Thus in ulcerative colitis and in the course of therapy with “broad spectrum” antibiotics “conditioned” deficiency states are hazards which should be anticipated by appropriate prophylaxis.

*Pyridoxine.* This substance is undoubtedly important in human metabolism. As a phosphorylated compound it takes part in the reactions controlled by the transaminase group of enzymes. However, there is no evidence that deficiency states ever occur in man, probably because his needs are fully met by synthesis. Pyridoxine has been tried in doses of 50-200 mg. for the treatment of irradiation sickness, hyperemesis gravidarum and agranulocytosis, but evidence of its therapeutic value in these and other disorders is still lacking.

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*Pantothenic Acid.* This vitamin appears to be necessary for the maintenance of health in certain experimental animals. In man the "burning feet" syndrome common in prisoner-of-war camps in the East was said to be wholly or partly attributable to pantothenic acid deficiency. There are no records of controlled observations which support the view that pantothenic acid has therapeutic value in man.

*Biotin.* In experimental animals biotin deficiency produces well-defined effects, but early reports of the occurrence of similar states in man remain unconfirmed. Biotin has no accepted therapeutic uses.

As mentioned above it is often best in prophylaxis and treatment of states of *Vitamin B complex* deficiency to administer the important members of the group together. Suitable preparations for this purpose include: Tablets of Yeast 0.3 G. Four tablets are taken at mealtimes three or four times daily. Aneurine Compound Tablets are also available, and each contains aneurine hydrochloride 1 mg., riboflavine 1 mg. and nicotinamide 15 mg. Higher doses are conveniently given by prescribing Aneurine Compound Tablets, Strong, each of which contains aneurine hydrochloride 5 mg., riboflavine 2 mg., nicotinamide 20 mg. and pyridoxine 2 mg.

### ASCORBIC ACID (VITAMIN C)

As long ago as the beginning of the 17th century John Woodall (1569-1643), a surgeon to Queen Elizabeth, was aware of the value of "the juice of vegetables and fruits" as a preventive against scurvy. The classic work on this subject, however, was written by James Lind in 1753. The chemistry of Vitamin C (ascorbic acid) was elucidated by several workers between 1920 and 1932 - but notably by Szent-Györgyi who isolated the compound from the adrenal gland as well as from cabbage and orange.

*Sources.* Ascorbic acid is found in most fresh fruits and vegetables, especially black currant, orange, lime, lemon, tomato, rose hips, fresh green vegetables and potato. Although the potato is not rich in Vitamin C, it is important because large quantities



are eaten. Many species in the animal kingdom can synthesise ascorbic acid but man is unable to do so—at any rate to a significant extent.

*Chemistry.* Ascorbic acid is a simple organic molecule easily synthesised from sorbose. The pure substance takes the form of colourless crystals, soluble in water and unstable on heating or in the presence of alkali. Hence Vitamin C is easily destroyed in cooking, and the quantity in many vegetables diminishes during storage.

**PHYSIOLOGICAL FUNCTIONS: SYMPTOMS OF DEFICIENCY.** A potent reducing substance, ascorbic acid is believed to take part in many reversible oxidation-reduction reactions, especially in amino-acid metabolism. It is essential for maintaining the integrity of the intercellular cement substance, and it has a part to play in erythropoiesis and in carbohydrate metabolism. Adult scurvy occurs when the diet is continuously and grossly deficient in Vitamin C for several months. This may be brought about by poverty, isolation, ignorance, or excessive restriction in the choice of foodstuffs on account of the therapeutic regimen. The symptoms and signs of scurvy as it affects adults and infants are detailed in textbooks of medicine. Although scurvy is a comparatively rare disease it still occurs among inmates of lodging houses in industrial cities. The victims are nearly always elderly men living on a diet of meat pies and tea. They are usually in poor general health, grossly anæmic, often œdematous, and show "sheet hæmorrhages" and brawny swelling of the legs especially behind the thighs. In infants scurvy may occur between 6 and 18 months especially in bottle-fed babies; characteristic features are anæmia and extremely tender subperiosteal hæmorrhages.

*Daily Requirement.* The requirement of the adult is estimated at 30 mg. daily and rather more than this during pregnancy and lactation and during illness caused by infection. The pure substance is readily available and bio-assay is therefore unnecessary.

*Absorption, Fate and Excretion.* Ascorbic acid is well absorbed from the intestine and from injection sites. Distribution occurs to

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all tissues and there is a slow destruction by oxidation throughout the body. Stores of ascorbic acid in the tissues are conserved by a renal threshold mechanism: free excretion in the urine occurs when plasma values over about 1.4 mg. per cent are reached. The utilisation of Vitamin C is increased in infection, and this may be important in a chronic illness, for example in tuberculosis.

*Preparations and Dosage.* Ascorbic Acid Tablets in 25 mg., 50 mg., 100 mg. and 200 mg. strengths are available. The prophylactic dose is 25-75 mg. daily and the therapeutic dose is 200-500 mg. daily; Injection of Ascorbic Acid contains 50 mg. per ml. and the dose is 2-5 ml. intramuscularly; Ascorbic Acid Tablets for Infants contain 5 mg. in each tablet.

**THERAPEUTIC USES.** The prevention of scurvy is normally a matter of providing a nutritious mixed diet with appropriate amounts of fresh fruit and vegetables; supplements of fresh fruit juice are valuable additional sources, and are often taken in any case as appetising beverages. In the treatment of scurvy 1 G. daily may be given for about a week and then 200 mg. daily for a month; and at the same time the patient is educated in the elementary principles of dietetics.

Ascorbic acid is sometimes administered with iron in the treatment of anæmia (p. 65). In the management of methaemoglobinæmia the potent reducing action of therapeutic doses of ascorbic acid is of value. In the many other clinical states for which treatment with ascorbic acid has been tried, there is no evidence that the treatment is of therapeutic value.

## CHAPTER 6

# DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

INTRODUCTION. The actions of drugs on the autonomic nervous system are described as far as possible in terms which belong to anatomical and physiological studies. Special importance is attached to the arrangement in the body of the main ganglia of the autonomic nervous system, the course and distribution of preganglionic and postganglionic nerve fibres, the influence of the mid-brain on the activity of the peripheral parts of the autonomic nervous system, and the interplay of endocrine and autonomic function. This kind of analysis is an essential part of any attempt to understand the end-result of giving a drug which affects the autonomic nervous system. At the same time, the student of clinical medicine must be alert to the dangers of oversimplification inherent in neat explanations. The different factors which make up the composite phenomenon called "pharmacological action" are necessarily evaluated on laboratory animals and on man. It does not follow that an action thus demonstrated and analysed is reproducible in the diseased human being, or that such actions as do occur are necessarily of therapeutic value. Allowance must be made for the many variables which accompany any biological experiment. And, paradoxically, due regard must be paid to the tendency of the organism to restore the *status quo*: even in disease man retains the power to defend himself against pharmacological assault and tends to re-establish situations temporarily disturbed by "therapeutic" intervention.

As would be expected, the division or classification of function within the autonomic nervous system (ANS) has the greatest significance for the pharmacologist when it is related to physiological rather than anatomical considerations. The division refers to two functional types of postganglionic nerve fibres—(a) the adrenergic and (b) the cholinergic. These correspond approximately to the anatomical divisions (a) *sympathetic* or dorsal; and

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(b) *parasympathetic* or craniosacral. The anatomical classification had little significance for the pharmacologist when it was shown that some parts of the sympathetic division are cholinergic. The physiological division is clearly to be preferred because it aims at identification of different structures in the autonomic nervous system in terms of function rather than by reference to their position in the body.

A tissue cell is commonly innervated from both divisions of the autonomic nervous system; and as cholinergic activity and adrenergic activity are largely antagonistic, the behaviour of the cell at a particular time depends to a considerable extent on which of these extrinsic influences is predominant. The effects of cholinergic and adrenergic activity on the different systems and tissues of the body are described and tabulated in standard works on human physiology. All preganglionic nerve fibres (that is both sympathetic and parasympathetic) are cholinergic. Postganglionic nerve fibres however behave differently: those of the parasympathetic division are cholinergic but those of the sympathetic division are adrenergic. In brief, therefore, it is helpful to consider the outcome of activity of the peripheral—or “effector”—parts of the autonomic nervous system as either (a) *sympathomimetic*—resembling the effects of administering adrenaline, or (b) *parasympathomimetic*—resembling the effects produced by the release of acetylcholine in the body. Adrenaline (or noradrenaline) and acetylcholine acting in relation to the autonomic nervous system as *chemical transmitters* are well described as *neurohormones*. The same type of mechanism operates in the distribution of the cerebrospinal nerves; acetylcholine is used as the chemical transmitter at the end-plates of the lower motor neurones where these terminate on the fibres of voluntary muscle.

A number of substances are known which, though not suitable for use in medical practice, are of great interest to pharmacologists and to clinicians: their selective action has helped to define the functions of various parts of the autonomic nervous system and—to a lesser extent—of the cerebrospinal nerves. The procedure also serves as a reminder that the separation of physiology, experimental pharmacology and clinical pharmacology is in fact artificial however convenient it may be.

MUSCARINE is an alkaloid obtained from the poisonous fungus *Amanita muscaria* (the fly fungus). Its pharmacological action is indistinguishable from that produced by stimulation of the postganglionic fibres of the parasympathetic division of the ANS or the effect of widespread release of acetylcholine in the tissues. Such is the action on smooth muscle, cardiac muscle, and on glands (exocrine glands) that in referring to the effects of acetylcholine on these structures it is customary to call them "the muscarinic actions".

NICOTINE is a colourless liquid alkaloid obtained from the leaves of the tobacco plant, *Nicotiana tabacum*. On absorption it has a direct action on all ganglia (sympathetic and parasympathetic) of the ANS: first it enhances the activity of the ganglia—so that they become more responsive to acetylcholine released at the preganglionic synapses; but this is followed by the characteristic *paralysis* of the ganglia, so that they become entirely unresponsive to preganglionic stimulation or to the local release of acetylcholine. Even when this effect on ganglia is fully established there is no interference with transmission in the postganglionic nerve fibre. The nicotine action is so consistent that the alkaloid can be used as a method of confirming the presence or absence of a synapse in an autonomic ganglion: if the application of nicotine blocks the passage of an impulse the interruption can be confidently attributed to the specific effect of the alkaloid on the synaptic junction of a preganglionic fibre with an autonomic ganglion; if the impulse is not blocked, it can be assumed that the fibre does not end in a synapse within that ganglion.

The typical blocking action of nicotine is evidently attributable to interference with physiological processes—in which acetylcholine is involved—at the preganglionic synapses. Reference has already been made to the part played by acetylcholine at the neuromuscular end-plates of the cerebrospinal nerves. It is therefore not surprising to find that nicotine can disorganise the activity of voluntary muscle: this action is similar to that of curare—the classic blocking agent which causes flaccidity of skeletal muscle. It must be added that although the action of nicotine on skeletal muscle can be anticipated from its blocking action on acetyl-

## DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

choline liberated at the preganglionic synapse, there are important quantitative differences. The block produced at the ganglia is intense, whereas the effect on skeletal muscle is weak; and the opposite is true of curare.

The varying effect of nicotine (according to the dose used) on ganglia and on skeletal muscle can also be reproduced by using appropriate concentrations of acetylcholine, and these actions are therefore described as the nicotinic effects of acetylcholine.

Finally there are drugs which can be used to block selectively the actions of acetylcholine as these are classified above. Drugs of the atropine group (p. 120) block the muscarinic actions of acetylcholine. Curare blocks the nicotinic actions of acetylcholine—particularly on skeletal muscle. Nicotine itself in *high concentration* blocks the “nicotinic actions” of acetylcholine on ganglia. Similarly, there are drugs which block adrenergic impulses or diminish the responsiveness of cells innervated by postganglionic sympathetic nerve fibres.

Nicotine is not used in clinical practice. However, the alkaloid has important practical applications which are dependent on its specific pharmacological actions: it is used as an insecticide—usually as a spray or mist. When nicotine is employed in this way by horticulturists, precautions are necessary to prevent serious poisoning. If a strong solution of nicotine is slopped on to the clothing the alkaloid passes readily through the skin and may kill rapidly by its effect on the respiratory centre—stimulation followed by depression. Toxic effects are also seen occasionally when a workman operating a spraying machine repeatedly inhales the mist heavily charged with nicotine.

## PARASYMPATHOMIMETIC DRUGS

An increase in the activity of tissues innervated by cholinergic nerves may be produced by: (1) *the choline esters*—acetylcholine, methacholine, carbachol and bethanechol; (2) *substances which inhibit cholinesterase*—physostigmine (eserine), neostigmine, diisopropylfluorophosphate (DFP) and edrophonium; (3) *the naturally occurring cholinergic alkaloids*, pilocarpine and muscarine.

I (a) ACETYLCHOLINE. Acetylcholine chloride is a white hygroscopic crystalline powder, soluble in water and decomposed by heat and alkalis. When cholinergic nerves are stimulated acetylcholine is released at the preganglionic nerve endings and also at the postganglionic nerve endings. This substance is also liberated at the endings of the adrenergic preganglionic nerves and the voluntary motor nerves. The actions of acetylcholine are classified as (a) *muscarinic* and (b) *nicotinic*. Muscarinic actions are those which can be reproduced by the injection of muscarine; they are all abolished by atropine. These actions correspond to those of acetylcholine released at the postganglionic nerve endings of parasympathetic and cholinergic sympathetic fibres. If an appropriate dose of atropine is given in order to block muscarinic effects, larger doses of acetylcholine produce other effects closely similar to those of nicotine. These nicotinic actions correspond to those of acetylcholine released at (a) the ganglionic synapses of the sympathetic and parasympathetic systems, (b) the junction of motor nerve with voluntary muscle, and (c) the endings of the splanchnic nerves around the secretory cells of the suprarenal medulla. This last action is sometimes separately classified as an "epinephrine mobilisation effect". The nicotinic actions of acetylcholine are blocked by curare, and by nicotine itself *in large doses*.

Acetylcholine acts directly on effector cells to elicit characteristic responses and in the case of muscle and ganglion cells this action is initially one of depolarisation of the postsynaptic membrane. Acetylcholine has only a transient action because it is hydrolysed to acetic acid and choline by cholinesterase—an enzyme present in the blood and other tissues. The action of this enzyme is inhibited by physostigmine and neostigmine. Hence these substances prolong and intensify the actions of injected acetylcholine. A great deal of useful information has become available from observing the effects of intravenous injection of acetylcholine and its more stable esters into laboratory animals. Only a limited number of observations have been made on the effects of these preparations when given intravenously *in man* because the procedure is very dangerous—so much so that it has been abandoned in medical practice.

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In man even large doses of acetylcholine can be given orally without producing any effect: it is so quickly destroyed in the alimentary tract that none can be absorbed. However, if acetylcholine is injected intravenously, striking pharmacological actions are quickly produced: the skin becomes flushed and there is a feeling of warmth; throbbing is felt in the head. There is increased sweating, lachrymation and salivation. With full doses a sensation of constriction develops in the chest. In the alimentary canal there is an increase of muscle tonus and peristaltic activity is more vigorous; gastric and intestinal secretions are more abundant; nausea, vomiting and evacuation of the bowel are common. Bronchospasm may be intense and is accompanied by increased bronchial secretion. The effects on the heart rate and blood pressure vary with the amount of acetylcholine given intravenously: characteristically bradycardia occurs and there is a fall in blood pressure. All these effects are transient and readily blocked by atropine.

Successful termination of attacks of supraventricular paroxysmal tachycardia by intravenous injection of 20-100 mg. of acetylcholine is certainly possible as a result of suddenly increasing vagal inhibition, but as already stated, intravenous medication with acetylcholine is contra-indicated: safer, more stable, compounds are used in clinical practice.

(b) METHACHOLINE CHLORIDE (Methylcholine Chloride). This substance is a colourless or white deliquescent crystalline powder. It is soluble in water and has a bitter taste. Its action in the body is qualitatively identical with that of acetylcholine, but it is less readily hydrolysed by cholinesterase and therefore has a more prolonged action. Methacholine chloride has much weaker nicotinic actions on autonomic ganglia.

The subcutaneous or intramuscular injection of 20 mg. of this drug to a normal subject causes a transient fall in blood pressure and compensatory tachycardia, salivation, sweating and flushing of the face also occur. This dose of the drug causes an increase in tone in the wall of the alimentary canal, vigorous peristalsis in the gastro-intestinal tract, and also stimulates secretion of gastric and pancreatic juice. The urinary bladder contracts and the sphincter relaxes. Methacholine also produces constriction of the



bronchi and increases bronchial secretion. In asthmatic subjects a typical attack is likely to follow the injection of methacholine. When methacholine is given by mouth the dose is 10-20 times greater than the subcutaneous dose.

The main *therapeutic indications* for methacholine chloride are supraventricular paroxysmal tachycardia, Raynaud's disease and abdominal distension. In supraventricular paroxysmal tachycardia the simpler methods should be used first, such as pressure on the eyeballs and pressure on the carotid sinus alternately. If these are unsuccessful then methacholine may be given subcutaneously. The patient should be resting and under medical supervision while he receives this treatment. A bedside commode should be available to enable him to have his bowels moved, if necessary, with minimum inconvenience. A usual dose is 20 mg. and sinus rhythm is commonly restored when the skin flush is most intense. If the injection does not succeed a second may be given in 30 minutes.

In severe cases of Raynaud's disease in which there is excessive constriction of the peripheral arterioles, methacholine given by mouth in doses of 200 mg. may give temporary symptomatic relief by producing vasodilatation.

A subcutaneous dose of 20 mg. will relieve patients suffering from abdominal distension due to postoperative ileus; but neostigmine is more commonly employed because its effect is more sustained and more readily adjusted to the needs of the individual patient. Posterior pituitary extract is to be preferred as an intestinal carminative.

(c) **CARBACHOL** (Carbamylcholine chloride). Carbachol is a white odourless crystalline powder soluble in water. This substance is a parasympathomimetic agent. It possesses nicotinic actions on autonomic ganglia. Unlike methacholine, it is not susceptible to hydrolysis by cholinesterase. In man, the injection of 0.5 mg. causes a warm sensation, flushing of the face, sweating, lachrymation and salivation. There may be mild intestinal cramps and a desire to empty the bladder. The effect of carbachol on the bladder may be used to relieve urinary retention following surgical operations, childbirth and—with caution—in elderly ill patients whose

## DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

weakness may prevent micturition. Before administering carbachol it is imperative to confirm that there is no obstruction to the outflow of urine. Carbachol has also been employed in peripheral vascular disease. It is usually injected subcutaneously in a dose of 0.25-0.5 mg., but 1-4 mg. can be given orally.

(d) **BETHANECHOL** (Urecholine). Bethanechol is available as the chloride. It is methylcholine carbamate. The dose is 10-30 mg. by mouth or 2.5-5 mg. if injected subcutaneously. Like carbachol, this substance is not hydrolysed by cholinesterase. It produces mainly muscarinic effects on the urinary bladder, the gastro-intestinal tract, and in the eye. These actions are abolished by atropine. This substance is used in urinary retention, abdominal distension and in gastric dilatation following vagotomy.

2 (a) **PHYSOSTIGMINE** (Eserine). Physostigmine is an alkaloid obtained from the Calabar bean: it is conveniently used in the form of the salicylate—a white, odourless, bitter, crystalline powder soluble in water and in alcohol. Physostigmine inhibits the destructive action of acetylcholinesterase and thus the effect of acetylcholine is prolonged. It has therefore not only a muscarinic action on smooth muscles, secretory glands and the heart, but also a nicotinic action on striped muscle and autonomic ganglia.

The main actions of physostigmine which are used in therapeutics are those on the eye and the intestine. When applied locally to the conjunctiva physostigmine causes (a) constriction of the pupil by intensifying the action of the parasympathetic nerves which control the sphincter pupillæ; (b) contraction of the ciliary muscle (also supplied by the parasympathetic) with consequent relaxation of the suspensory ligament of the lens—which accordingly becomes more convex and fixed to accommodate *near* objects only. When the ciliary muscle contracts in response to physostigmine, it may go into spasm and this causes considerable pain in the eye. The characteristic effects of physostigmine are well established in a few minutes and are maximal in about 30 minutes. It may take from 1 to 3 days for the pupil to return to its normal size. Intense contraction of the pupil is of course accompanied by full extension of the iris, and this has important

effects on intra-ocular pressure. In this state, the cribriform spaces of Fontana are widened and filtration from the anterior chamber of the eye into the canal of Schlemm is facilitated. Thus, if the intra-ocular tension is excessive—as in glaucoma—the use of physostigmine is often of great value in tending to reduce pressure in the anterior chamber.

The effects of over-activity of parasympathetic innervation—as described above (see acetylcholine) are reproduced by the administration of physostigmine. Clinically the most important of these are intestinal colic and sometimes evacuation of the bowel, excessive salivation, lachrymation and bronchorrhœa.

In clinical practice physostigmine is used in glaucoma to reduce intra-ocular pressure. It is also employed alternately with atropine to break down adhesions between the iris and the lens or cornea—a procedure sometimes called “iris gymnastics”.

In paralytic ileus following operations or in the distension of the bowel in acute infection physostigmine may be used hypodermically in a dose of 1-2 mg.; or 1 mg. of physostigmine may be combined with 0.5 ml. of Extract of Posterior Pituitary (injected separately).

In the treatment of intestinal ileus, either physostigmine or neostigmine can be used as an ancillary to general measures: neostigmine is preferred for this purpose because its action on the bowel appears to be more selective than that of physostigmine.

(b) **NEOSTIGMINE METHYLSULPHATE** is a white, crystalline powder; it is soluble in water and is used for parenteral administration. Neostigmine Bromide is similar in physical characteristics and is given by mouth in tablet form. The usual parenteral dose is 0.5-1 mg.: the doses given orally are 15-45 mg. Neostigmine has a marked anticholinesterase activity, and by reason of this enzyme inhibition it exerts its parasympathomimetic actions. In addition to this, neostigmine possibly has a direct stimulant action on voluntary muscle.

Substances like physostigmine and neostigmine inhibit the action of cholinesterase by competing with acetylcholine for the enzyme. The combination of these drugs with the enzyme is a reversible reaction. Neostigmine has a more selective action than

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physostigmine and particularly influences the urinary bladder and the gastro-intestinal tract. The muscarinic effects of neostigmine are blocked by atropine and the nicotinic effects by curare and nicotine. •

Neostigmine increases the frequency and amplitude of the gastric contractions; it also stimulates the secretion of gastric juice. Motor activity is also increased in the lower portions of the oesophagus and in the small and large bowel. Ureteral peristalsis is stimulated and evacuation of the bladder commonly occurs. Neostigmine produces bradycardia.

Myasthenia gravis is a comparatively rare disease affecting skeletal muscle. It is attributable to a disorder of neuromuscular transmission: for reasons which are still not entirely clear, there is premature exhaustion of the normal mechanisms which permit of prolonged muscular activity. Fatigue and muscular weakness develop as though the patient lacked adequate supplies of acetylcholine at the motor nerve end-plates; or alternatively as though some local abnormality of the motor end-plates prevented the prompt use of normal supplies of acetylcholine. Whatever may be the correct explanation of this disorder, there can be no doubt about the effectiveness of inhibitors of cholinesterase such as neostigmine in abolishing the symptoms. In severe cases a patient may become almost prostrate: the clinical picture is described in textbooks of medicine. Within a minute of receiving an appropriate dose of neostigmine, all the symptoms and signs may be abolished. The transformation in the appearance and the capabilities of such patients is one of the most remarkable phenomena in therapeutics and provides a classic lesson in the physiology and pharmacology of neuromuscular transmission.

Applied locally to the eye neostigmine produces a small pupil, but the drug given orally or parenterally has no significant effect on the eye. On intravenous injection neostigmine (0.5-1 mg.) rapidly antagonises the autonomic ganglion-blocking substance, tetraethylammonium.

In clinical practice, neostigmine is used to relieve abdominal distension (0.5-1 mg. subcutaneously), but before the drug is injected it is wise to confirm that the rectum is empty; a rectal tube left *in situ* facilitates evacuation of flatus. Neostigmine has

also been recommended for the prevention of postoperative intestinal atony and here 0.25 mg. is given subcutaneously 2-3 hours after the operation and continued 6-hourly for 2-3 days. It can be given orally to increase the peristaltic activity of the bowel in old people who have developed faecal impaction in the rectum but, of course, the rectum is first emptied digitally or by enema. The usual dose is 15 mg. by mouth 4 times a day, gradually cutting this down until it can be discontinued. It is also employed in myasthenia gravis and in this instance the dose varies with the severity of the disease. Oral therapy is employed wherever possible, with the rough guide that a dose of 15 mg. of the bromide by mouth is equivalent to 0.5 mg. of the methylsulphate injected subcutaneously. Side-effects may be minimised by taking the drug with food to delay absorption; or 0.6 mg. of atropine sulphate 2 or 3 times daily may be necessary. Neostigmine is also of value in the diagnosis of myasthenia gravis. The dramatic improvement in muscle power is diagnostic of myasthenia gravis, provided that an injection of an inert solution (normal saline) has first been shown to be without beneficial effect.

Neostigmine methylsulphate is an antidote to tubocurarine. It inhibits the action of cholinesterase and thus, notwithstanding the state of block caused by tubocurarine, the increased concentration of acetylcholine restores the ability of the muscle to contract. The instillation of 2.5 per cent solution of Neostigmine Bromide into the conjunctival sac reduces intra-ocular tension in glaucoma.

(c) DI-ISOPROPYLFLUOROPHOSPHONATE (DFP) and Tetraethyl Pyrophosphate (TEPP) are powerful inhibitors of cholinesterase. They differ from physostigmine in that they inhibit the enzyme irreversibly and thus their effects in the body are much more prolonged. DFP has been used to increase intestinal activity in the treatment of postoperative ileus. This preparation is dispensed in arachis oil because in aqueous solution it hydrolyses and produces a toxic vapour containing hydrogen fluoride. In glaucoma DFP is applied in solution in arachis oil (0.1 per cent): it is undoubtedly effective in some cases, but early claims that DFP is materially superior to physostigmine are open to doubt.

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(d) **EDROPHONIUM** ("TENSILON"). This is a white crystalline powder soluble in water. It is a quaternary ammonium compound: its chemical structure shows its relationship to neostigmine. Edrophonium is a short-acting cholinergic drug, rapidly destroyed by cholinesterase. As such it is of no value in therapeutics but it is of much interest for diagnostic purposes. If a patient is suffering from muscular weakness edrophonium can be used in tests which are of short duration and which have a sharp end-point. An additional advantage is the fact that the effect of this drug on skeletal muscle is more prominent than upon autonomic ganglia or cholinergic visceral receptors. Following an injection of edrophonium, the myasthenic patient (myasthenia gravis) experiences immediate but fleeting increase of muscle power. In a case of proved myasthenia gravis under treatment with neostigmine, if the use of an edrophonium supplement increases muscle power the conclusion is that the dose of neostigmine should be somewhat increased; if the test is negative (no increase in power) there is no justification for increasing the dose of neostigmine. Edrophonium is, of course, an effective curare antagonist.

3 (a) **PILOCARPINE**. This alkaloid is obtained from the leaves of various species of the shrub of *Pilocarpus* from South America. The nitrate is the salt usually employed therapeutically - -shining colourless crystals, soluble in water. The dose is 3-12 mg. hypodermically or by mouth.

This drug has a highly selective action on the reactive substance of cells innervated by postganglionic cholinergic fibres. It thus produces most of the muscarinic effects of acetylcholine. The sweat and salivary glands respond very actively to pilocarpine resulting in profuse sweating and salivation. Secretion in the stomach and in the mucosa of the respiratory tract is also increased. When applied locally to the eye, pilocarpine produces contraction of the pupil; accommodation is fixed for near vision, and there is a transitory rise in intra-ocular pressure followed by a more persistent fall. Pilocarpine is sometimes used as an alternative to physostigmine for the treatment of glaucoma and in breaking down of adhesions between iris and lens by alternating

this treatment with the use of atropine. The use of ganglion-blocking agents such as mecamlamine and pentolinium (p. 163) has created a new use for pilocarpine. The side-effects of these hypotensive drugs on ocular accommodation, salivation and intestinal activity can be wholly or partly controlled by the stimulating effect of pilocarpine on the peripheral parasympathetic

(b) MUSCARINE. (See p. 110.)

## PARASYMPATHETIC DEPRESSANTS WHICH ACT PERIPHERALLY

### BELLADONNA SERIES AND ATROPINE SUBSTITUTES

INTRODUCTION. A number of important alkaloids are found in the leaves of the well-known plant, the Deadly Nightshade (*Atropa belladonna*); and there are several other sources. These active principles, known as the Atropine Group of alkaloids include hyoscyamine, atropine itself (*d-l*-hyoscyamine), hyoscyne, and belladonnine. The most important pharmacological action which they have in common is that of blocking the actions of acetylcholine. The effects of giving a drug of the atropine group can therefore be anticipated: they closely resemble those which would result from widespread depression of the parasympathetic nerves (cholinergic nerve endings). A state of imbalance between sympathetic (adrenergic) and parasympathetic (cholinergic) activity in the autonomic nervous system becomes apparent: cholinergic activities are in abeyance and those which are adrenergic become more obvious. This characteristic effect of the atropine group of alkaloids is exerted at postganglionic cholinergic nerve endings. These drugs also affect the brain at different "levels" (medulla, mid-brain, cerebrum) and it is here that a contrast emerges: hyoscyne produces effects which are entirely different from those of atropine and hyoscyamine; these differences are discussed below.

Chemically the atropine group of alkaloids are organic esters formed by the combination of an aromatic acid (usually tropic acid) with complex organic bases either tropine or scopine. Homatropine is a synthetic compound produced by a combination of the

base tropine with mandelic acid. Atropine (racemic or *d-l*-hyoscyamine) is an ester of tropic acid and the tertiary amino-alcohol tropine. Like most alkaloids atropine is insoluble in water, and it is therefore used therapeutically as the water-soluble sulphate - a colourless, crystalline hygroscopic substance. It has two main actions: (1) it blocks activity at postganglionic cholinergic nerve endings to the body-tissues: thus it antagonises the muscarinic actions of acetylcholine and most of the effects of stimulation of parasympathetic and the *cholinergic* sympathetic fibres; (2) a single therapeutic dose has a mildly stimulating effect on the vital centres in the medulla and on the higher cerebral centres. The following effects can therefore be seen in various parts of the body.

THE EYE. (a) The effects here are the opposite of those produced by acetylcholine and physostigmine (p. 115). The constrictor nerves of the iris belong to the parasympathetic nervous system: their activity depends on the availability of acetylcholine at the nerve-ending; atropine renders these nerve-endings insusceptible to acetylcholine; the constrictor influence of the parasympathetic is thus removed and the pupil dilates under the influence of the sympathetic (adrenergic) nerve supply to the iris. (b) Under the influence of atropine, accommodation is "set" for infinity. This occurs because the lens becomes almost flat and non-refractive. The chain of events leading to this is as follows: block of the cholinergic nerve fibres supplying the ciliary muscle; relaxation of the ciliary muscle; tightening of the suspensory ligament of the lens; compression of the lens so that it becomes almost flat - a state in which only objects that are *remote* can be seen clearly. The effects of atropine on the pupil and on accommodation are observed no matter how the drug is administered - orally, parenterally, or by local application - but the intensity of effect and the degree of selectivity of the effect naturally vary with the method employed. Pupillary dilatation of some degree can also be produced by drugs which act as though they stimulate sympathetic nerve endings (adrenergic nerves) supplying the radial (dilator) muscle of the iris: these are the sympathomimetic amines (p. 134) such as ephedrine. The partial dilatation of the pupil which



they produce can be made *maximal* by the subsequent use of drugs of the atropine group. It is stated that intra-ocular tension in the *normal* eye is not increased by the use of atropine. Nevertheless it is wise to avoid the use of atropine in circumstances in which intra-ocular tension tends to be raised, for example in old people: safe mydriatics for such patients are the relatively mild ones in the sympathomimetic group.

**CARDIOVASCULAR SYSTEM.** If, by means of atropine, vagal inhibition of the cardiac action is rather suddenly diminished, there is naturally an increase in heart rate. This tachycardia is the characteristic effect of an injection of a therapeutic dose of the drug in man, and it is precisely what would be expected from current views on the function of the vagus in relation to cardiac action and the consequences of depressing vagal activity by means of cholinergic blocking agents of the atropine group.

It is interesting to note, however, that at certain low concentrations of atropine in the tissues there may be a fleeting period of slowing of the heart (bradycardia): it is probably the result of a direct stimulating action on the medullary vagal nuclei. This biphasic action is of considerable academic interest to the experimental pharmacologist—especially as it can also be demonstrated in other organs and tissues—but from the clinician's viewpoint this phenomenon is unimportant because it is too inconstant and too transient to have therapeutic significance.

After a moderate dose of atropine the heart rate usually increases by about 30 beats per minute. In infants and in old people, however, the increase may be much less—one sign of the greater tolerance of the very young and the very old to atropine.

Therapeutic doses of atropine have no effect on blood pressure. Toxic doses cause (among other things) widespread flushing of the skin because of relaxation of the arterioles and dilatation of the capillaries: this may be the result of depression of the vasomotor centre or due to a peripheral vasomotor paresis.

**RESPIRATORY TRACT.** Atropine reduces mucosal secretion in the nose, mouth, pharynx and bronchi. This produces a sense of dryness in the mucous membrane of the respiratory tract. The

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smooth muscle of bronchi and bronchioles tends to relax as a result of vagal inhibition.

**GASTRO-INTESTINAL TRACT.** When full doses of atropine are given the peristaltic movements of the stomach, small bowel and colon are inhibited and this is accompanied by a reduction in tone. The total volume of gastric juice and the total acid content are decreased. The secretion of saliva is markedly inhibited by atropine and "dryness" of the mouth is one of the most conspicuous and troublesome side-effects. No significant change is noted, however, in the intestinal and pancreatic secretions; nor does the output of bile appear to be affected.

**OTHER ACTIONS OF ATROPINE.** Under the influence of full doses of atropine there is a reduction of muscle tonus in the kidney pelvis and ureter, and peristaltic movement along the ureteric canal becomes relatively weak and infrequent. It abolishes contractions of the urinary bladder produced by parasympathomimetic drugs; and when the detrusor muscle is in a state of hyper-tonus, it is relaxed by atropine. Atropine has a mild spasmolytic action on the gall bladder and bile ducts. The secretion of the sweat glands is inhibited. Dryness of the skin after substantial doses of atropine is sometimes an undesirable side-effect when drugs of the belladonna group are used therapeutically—for example in patients with peptic ulcer. Occasionally, patients suffering from bouts of sweating obtain symptomatic relief from small doses of atropine. Pharmaceutical preparations made from belladonna leaf are of course quite reliable for therapeutic purposes. The most important differences are those which are apparent between a crude drug on the one hand and its active principle on the other. If the *doses* are comparable the effects observed are quantitative and are related to rates of absorption and the tissue concentrations which are achieved. As already stated belladonna leaf contains other alkaloids—in addition to atropine; but when belladonna preparations are administered therapeutically the total effects do not differ qualitatively from those produced by an equivalent amount of atropine. It was formerly held that the spasmolytic effects of drugs of the atropine

group are most readily obtained by giving hyoscyamus, but this is one of the "clinical impressions" which await confirmation by clinical trial. The *prima facie* case for such a view is not convincing.

It is sometimes desirable to exhibit drugs of the atropine group in amounts far exceeding pharmacopoeial doses, for example in the symptomatic treatment of Parkinsonism. This can be done by gradually increasing the dose at intervals of two or three days: the human subject appears to have a remarkable capacity for acquiring tolerance to this group of alkaloids.

Minute amounts of atropine and kindred alkaloids are absorbed by the skin when belladonna is applied - for example as a plaster. However, the use of belladonna in this way is irrational; and such local benefit as may be derived from the plaster cannot be attributable to the topical effects of the alkaloids. The repeated application of a solution of atropine sulphate or a similar preparation to a mucosal surface may, however, produce systemic effects easily identified by the patient's complaining of "dryness" of the mouth: this applies especially to the use of atropine as eye-drops. When taken by mouth the belladonna alkaloids are absorbed rapidly from the alimentary tract: the speed of onset is largely determined by whether the drug is given to the patient in the fasting state or immediately after a meal. These alkaloids are mainly destroyed in the liver, but traces are excreted in the urine.

**TOXIC EFFECTS.** Overdosage with atropine or belladonna produces dryness of the mouth and intense thirst: difficulty in swallowing and in talking are consequences of this total cessation of mucosal secretion. Vision is blurred because of complete paralysis of accommodation. The pupils are widely dilated. The skin is flushed, dry and hot. The heart rate is rapid. The patient is restless, confused and may show muscular incoordination. His mental state may warrant a diagnosis of acute toxic psychosis accompanied by hallucinations. Respiratory failure from depression of the medullary centres may be fatal. If some of the poison is thought to be still in the stomach gastric lavage is indicated, but clearly this treatment is not required if the drug was not taken by mouth. The pharmacological antidote is a parasympathomimetic drug, and neostigmine methylsulphate 5 mg. is the pre-

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paration used. In severe poisoning where atropine block of the peripheral parasympathetic is intense, neostigmine and its allies may fail to reverse the atropine effect, but several doses should be given—at intervals of about one hour—before regarding the condition as intractable. Much benefit is derived from the use of sodium phenobarbitone injected intravenously in doses which just suffice to abolish restlessness and delirium.

### THERAPEUTIC USES

Atropine Sulphate is the preparation in common use and can be given orally as a tablet or subcutaneously or if necessary intravenously; the BP dose is 0.25–1 mg. Tincture of Belladonna is made from the leaves of *Atropa belladonna* and is widely used. The dose recommended in the BP is 0.3–1 ml. A useful alternative is the Dry Extract of Belladonna and this is available as a Tablet (BNF) containing 15 mg. of the extract: an average dose is 2 tablets.

Atropine and belladonna are used mainly for their sedative and spasmolytic effects on the gastro-intestinal tract. Full doses are recommended in the medical treatment of peptic ulceration -to diminish gastric peristalsis, relieve local spasm, and decrease acid secretion. Drugs of this group are used also to give relief in pylorospasm. In congenital hypertrophic pyloric stenosis of infants much reliance is placed on the spasmolytic effects of atropine methonitrate (Atropine Methonitrate Solution, BNF, which is a 1 in 10,000 solution: dose 1 ml. increasing to 5 ml. per dose). In certain abnormal conditions of the bowel - irritable colon, ulcerative colitis and the dysenteries painful spasm may be relieved by the spasmolytic action of atropine. When chronic constipation is thought to be attributable to a spastic state of the bowel, belladonna may be of value. If morphine is used to combat pain in acute cholecystitis there may be sudden intensification of symptoms as a result of morphine-induced spasm of the sphincter of Oddi. In anticipation of this, many clinicians give atropine sulphate simultaneously- mixing the dose with the morphine in the syringe.

Where heart block is due to depression of the auriculo-ven-

tricular bundle through vagal stimulation, atropine in full doses of 1-2 mg. intravenously may restore normal sinus rhythm. Occasionally fainting or dizziness is caused by a hypersensitive carotid sinus; atropine sulphate may abolish the symptoms by blocking some of the vagal impulses affecting the carotid sinus.

Atropine is widely used before the administration of a general (inhalation) anæsthetic: it keeps the respiratory passages free from secretion which might impede the passage of air. In severe cases of whooping cough tincture of belladonna in full doses may help to reduce the number of severe paroxysms.

In nocturnal enuresis in children, atropine may be of value by relaxing the hypertonic bladder. It is also given with morphine in colic which accompanies the passing of a stone down the ureter. In the rigidity and tremor of Parkinsonism relief may be obtained by giving full doses of belladonna. Preliminary administration of small doses of atropine may prevent any side-effects due to neostigmine in the treatment of myasthenia gravis.

Local applications of atropine are of great value in the treatment of diseases of the eye. When alternated with miotics, the mydriatic action of this drug can be used to break down early adhesions between the lens and iris in such conditions as acute iritis, iridocyclitis and keratitis. The danger of precipitating glaucoma must always be kept in mind when atropine is instilled into the eye: the risk is a very real one in old people.

**HYOSCINE (SCOPOLAMINE).** Hyoscine is an alkaloid obtained from the flowers of various species of solanaceous plants: it is an ester of tropic acid and scopine. The preparation used is the alkaloidal salt Hyoscine Hydrobromide—colourless, crystalline and soluble in water. The BP dose is 0.3-0.6 mg. The similarities and the differences between the actions of hyoscine and atropine are of considerable importance in therapeutics. The gist of the matter is that both alkaloids block cholinergic activity: here the effect of hyoscine is more powerful but of shorter duration. On the brain a single dose of hyoscine produces depression—easily confirmed by the onset of *drowsiness*; a single dose of atropine does not cause drowsiness but a mild state of excitation—which may or may not be apparent. An excessive quantity of

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hyoscine produces a toxic psychosis with gross disorientation, delirium and coma; an overdose of atropine causes a psychosis marked by restlessness, excitement, mania, and finally coma—at the stage of exhaustion of the over-stimulated vital centres in the medulla.

After a small dose of hyoscine there is a degree of amnesia—clouding of the memory for recent events. For this reason it was formerly used with morphine to produce the state of 'Twilight Sleep' during childbirth: morphine diminished awareness of pain; hyoscine tended to abolish the recollection of unpleasant sensations. In skilful hands this was a valuable therapeutic procedure, but most obstetricians have abandoned it in favour of pethidine (p. 258). It must be emphasised that pharmacological doses of hyoscine have no analgesic action. Hyoscine, when properly used, is a most valuable prophylactic against travel sickness. A dose of 0.3 mg. is usually ample for an adult. It must be taken fasting—say 15 minutes before food—if a meal is taken prior to the journey. When dryness of the mouth is noted, it is safe to assume that the anti-emetic effect is also established. The action persists for 2–3 hours. If necessary one or two small doses (0.1 mg.) can be taken at intervals of 2 hours if the journey is prolonged. Doses in excess of this are apt to result in the state of 'Twilight Sleep' and even mild hallucinosis—and the effects are most disagreeable while travelling. For the same reasons, hyoscine is contra-indicated as an anti-emetic if the period of travelling extends over several days. It can however be used on two or three days of the week, thus allowing time for the metabolism and excretion of the drug. "Late travel sickness" sometimes supervenes if the drug is destroyed very rapidly in the tissues. In these circumstances "tapering doses" (0.05–0.1 mg.) can be used once or twice in the 24 hours following the journey. In brief, hyoscine prevents travel sickness but it should be used only for *journeys which last a few hours*.

In clinical practice hyoscine is used as a sedative to calm excited or maniacal patients; it is commonly combined with morphine—for example morphine 16 mg. and hyoscine 0.45 mg. In such circumstances some care is necessary if there is reason to suspect depression of the respiratory centre: morphine undoubtedly has a depressant action on the centre; it is no longer

held that therapeutic doses of hyoscine have this effect. It is convenient but not essential to inject both drugs simultaneously. A safe procedure is to give 0.3 mg. hyoscine intravenously and to note the sedative effect in about 15 minutes; at this stage a decision can be made about giving the morphine supplement, and in the absence of respiratory depression a half of the dose (up to 8 mg.) can be given by the intravenous route—to provide immediate information regarding the usefulness of the drug.

Preparations of hyoscyamus and of stramonium have the same action as atropine but are now less commonly used. Hyoscyamus is said to have a more powerful spasmolytic effect on the bowel and at one time was employed as a "corrective" to drastic purgatives. Stramonium has a reputation of being particularly effective in the treatment of Parkinsonism and also for relaxing the bronchi in asthma. As already stated, these claims still await critical examination and assessment.

**HOMATROPINE.** Homatropine is an alkaloid prepared from tropine and mandelic acid. It is used in the form of Homatropine Hydrobromide which is readily soluble in water and miscible with eye-ointment base. Its use is practically restricted to ophthalmic practice: it is a mydriatic, and its advantage over atropine is that it acts more rapidly and its effect is over well within 24 hours (the effect of atropine may last up to a week). Homatropine is therefore valued as a safe mydriatic for diagnostic work. It seldom increases intra-ocular tension significantly. The mydriatic effect can be increased by the addition of cocaine hydrochloride 1 per cent to the eye-drops.

**ATROPINE METHONITRATE.** The pharmacological actions of this preparation are essentially those of atropine. It is used therapeutically because it is stated to be less toxic than atropine, yet rather more effective as a spasmolytic and as a mydriatic. As stated above it is used in the treatment of congenital hypertrophic pyloric stenosis of infancy and in the relief of spasm in diseases of the alimentary tract in adults. As atropine methonitrate is unstable in aqueous solution, it can conveniently be administered as an alcoholic solution (0.6 per cent); 0.2 ml. contains 1 mg. of

atropine methonitrate and this can be absorbed through the buccal mucosa—a real advantage if the patient is vomiting.

**ATROPINE SUBSTITUTES.** Numerous synthetic anticholinergic drugs are now available. Their pharmacological actions are necessarily similar to those of the atropine group. The manufacturer's objective, however, is to create a new substance at least as valuable as atropine therapeutically, and also possessing material advantages such as relative freedom from side-effects. Precise assessment of the therapeutic merits of new preparations is satisfactorily determined only by clinical trials. It is noteworthy that many new anticholinergic drugs are recommended as symptomatic remedies for use in the management of patients suffering from gastrointestinal diseases. Special attention has been paid to these disorders because they are very common and tend to become chronic and relapsing in character. A few examples are mentioned below.

(1) *Peptic ulcer.* Much is known about the effects of the anticholinergic drugs on the motor and secretory functions of the stomach. This is not to say however, that all these pharmacological actions are necessarily significant in the therapeutic sense. No drug is known which acts directly on the ulcer to promote healing. It is part of the natural history of peptic ulcer that it tends to heal spontaneously. Drug therapy may however be directed towards creating conditions which favour more rapid healing; and also the patient's immediate symptoms are relieved. The most important single measure for relieving local pain and distress associated with peptic ulcer is the reduction of gastric acidity by means of alkalis or adsorbents (p. 404). Anticholinergic drugs are valuable adjuvants: they diminish gastric secretion, produce quiescence by inhibiting peristalsis, and (perhaps most important of all) they relieve local spasm which is often excited by a focus of irritation in the gastric or duodenal mucosa—such as an active ulcer. The delayed emptying of the stomach consequent on diminished tonus and motility indirectly reduces acidity by giving a longer time for the normal "mopping up" of acid by antacids and by protein foodstuff. The hormonal phase of gastric secretion is not altered by the administration of anticholinergic drugs.

(2) *Dumping syndrome.* After surgical removal of a large part of the stomach, postprandial symptoms of considerable severity may



occur: they are described collectively (though probably inaccurately) as the Dumping Syndrome. The distress felt by the patient may be caused by mechanical distension of the small intestine by the sudden shifting of foodstuff from the small pouch which is all that remains of the stomach. If this is the mechanism, the relief afforded by the anticholinergic drugs may be explained by their ability to cause relaxation of the intestine so that the lumen of the bowel can more readily accommodate the food.

(3) *Diseases of the Colon.* Among the symptoms of inflammatory disease in the colon are pain (continuous discomfort and colicky pain), distension and flatulence. Distress arising from these conditions is often alleviated by the use of anticholinergic drugs. The spasmolytic action and the tendency to produce quiescence of the bowel are the most important actions. These effects are of course merely palliative: other measures are needed to combat the cause of the inflammation.

#### CONTRA-INDICATIONS

The contra-indications to the use of powerful anticholinergic drugs are as follows:

1. *Urinary Retention.* Extreme care must be exercised where a patient—usually an old or middle-aged man—gives a history of urethral stricture or of prostatic hypertrophy.

2. *Glaucoma.* As acute glaucoma can be produced by these drugs, any history of ocular pain or recent visual disturbance (especially in an elderly person) provides a contra-indication.

3. *Coronary Artery Disease.* Atropine was formerly used as part of the treatment of acute coronary thrombosis. It was intended to block vagal impulses and thus to prevent coronary vasoconstriction. The positive advantages of this precaution are open to question. Further, the tachycardia which commonly follows the injection of a large dose of atropine may cause anginal pain and much distress.

4. *Pyloric Obstruction.* If there is organic disease resulting in pyloric obstruction and retention of gastric contents, they inhibit tonus and peristalsis and thus aggravate gastric stasis.

5. *Achalasia of the Cardia.* Clinical experience shows that the anticholinergic drugs have no place in the therapy of achalasia—

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in which there is failure of the cardia to relax. Dilatation by means of bougies is still the most reliable form of treatment.

6. *Drug Idiosyncrasy and Allergy.* Rashes have been reported following the use of belladonna and atropine. Other more serious side-effects have occasionally followed the use of the newer synthetic drugs. A curare-like reaction has occurred after oral methantheline; toxic psychoses have developed after other new preparations of this kind. The newer anticholinergics should be used with special care until more is known about these toxic and allergic effects.

### NEW ANTICHLINERGIC DRUGS

There are many groups of drugs which share a certain general pattern of pharmacological activity. The particular properties of the individual member of the group have always received close attention because, where peculiarities exist, they can often be exploited therapeutically. Among the anticholinergic drugs, the similarities and differences presented by the pharmacological actions of atropine and hyoscyne have already been mentioned (p. 126). A much wider field for exploration on these lines has been provided by the production of a large number of synthetic anticholinergics. The object of pharmaceutical research of this kind has been to create a group of compounds differing mainly in their side-effects, and to make appropriate therapeutic use of those preparations.

It is important to bear in mind that drugs deliberately synthesised for a particular purpose and "screened" by pharmacological techniques on isolated tissues and experimental animals have still to be assessed on the human subject, and submitted to well-designed clinical trials. There is already such a large number of synthetic anticholinergic drugs that no individual practitioner can hope to possess adequate clinical experience of them all. Indeed it is highly improbable that he will wish to add more than one or two of these preparations to the official remedies which provide a standard for comparison. His main concern is to answer the question: Is there reliable evidence that this new preparation is *therapeutically* superior to the standard preparations? Skill in the use of drugs comes from detailed knowledge of the actions and

potentialities of a limited number of pharmaceutical products.

From the clinician's viewpoint, the new synthetic anticholinergics may be classified as follows:\*

(i) SPASMOLYTICS:

(a) Adiphenine Hydrochloride ("Trasentin"); 75-100 mg. (tablets) twice daily.

It is selective enough to relieve the colic caused by neostigmin: without producing atropine-like effects elsewhere. Adiphenine is therefore used symptomatically in intestinal and biliary colic; it may be beneficial in dysmenorrhœa. This relaxant effect is partly due to a powerful papaverine-like action. Tablets should be swallowed, not sucked, as the drug is also a powerful local anæsthetic.

(b) Amprotropine Phosphate ("Syntropan"); 50 mg. (tablets) thrice daily.

Therapeutically this resembles (a) above: the atropine-like action is weak and the papaverine-like action strong.

(c) Diphehanil Methylsulphate ("Diphenatil") 50-200 mg. (tablets).

The blocking action of this drug is similar to that of atropine except that it is less apparent on the eye and on salivary glands. The action occurs not only at postganglionic nerve endings but also at all autonomic ganglia; but transmission at sympathetic ganglia is blocked only after large doses. Absorption from the alimentary canal is rather erratic. The drug has been used as an alternative to atropine as a spasmolytic in bronchial asthma, peptic ulcer and to check excessive sweating. By intramuscular injection the dose is 20 mg. 6-hourly.

(d) Propantheline Bromide ("Pro-Banthine") 15-30 mg.

This drug has been introduced as an alternative to methantheline ("Banthine"); the newer compound is a more potent anticholinergic and much less toxic. It blocks transmission at ganglion level as well as at the postganglionic nerve-endings. It is a powerful spasmolytic and deserves trial in patients with diseases of the alimentary canal where pain is attributable to muscle spasm. The side-effects are those of atropine, and excessive dryness of the mouth may be troublesome. Large doses produce curare-like effects (p. 232). This drug is contra-indicated if there is liability to glaucoma; in the presence of

\* After Martindale: *The Extra Pharmacopœia*, 1958, i, 198-199.

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prostatic enlargement the anticholinergic action may precipitate dysuria; and in pyloric stenosis there may be prolonged gastric stasis.

Other synthetic anticholinergic drugs in this group include 'Tri-cyclamol Methylsulphate' ('Elorine Methylsulphate'), Oxyphe-nonium Bromide ('Antrenyl'), and Penthienate Bromide ('Monodral').

(ii) The synthetic anticholinergics which are used *in ophthalmology* and possess advantages over atropine and homatropine (p. 128).

(a) *Eucatropine Hydrochloride* (USP) is used only as a mydriatic. A few drops of 5 per cent solution are used, and this is repeated in 5 minutes. Dilatation of the pupil occurs within half an hour and lasts about 4 hours. Accommodation is affected slightly or not at all. There are no local ill-effects.

(b) *Lachesine Chloride*. This resembles atropine in its effect on the pupil and on accommodation but it is only moderately powerful. It produces no ill-effects on the conjunctiva or the eyelids: the Eye-drops of Lachesine are a 1 per cent solution.

(c) *Dibutoline Sulphate*. This is used as a mydriatic and cycloplegic: its anticholinergic activities elsewhere, especially in the gastro-intestinal tract, make it a useful spasmolytic. Dibutoline sulphate (2.5 per cent) and homatropine hydrobromide (2 per cent) are often used together with good results and less liability to conjunctivitis.

(iii) Another group of compounds which are chemically related to atropine are used for their predominant *effects on mid-brain*: many are valuable alternatives to atropine and hyoscine in the treatment of Parkinsonism. They include Benzhexol Hydrochloride ('Artane'), Caramiphen Hydrochloride ('Parpanit'), and Procyclidine Hydrochloride ('Kemadrin'): they are dealt with elsewhere (p. 242), but it may be pointed out that the side-effects of the drugs are particularly significant in revealing their chemical relationship to atropine.

## SYMPATHOMIMETIC DRUGS

## ADRENALINE

Adrenaline is a white or light brown microcrystalline powder prepared from an acid extract of animal suprarenal gland or synthetically. It is slightly soluble in water and combines with acids to form very soluble salts; Adrenaline Solution (0.1 per cent) is in routine use. Adrenaline is unstable in neutral or alkaline solution; it is readily oxidised to inert substances.

Adrenaline and noradrenaline (p. 138) are released at sympathetic nerve endings and both are inactivated by enzyme systems which include amine oxidase.

By mouth adrenaline has no systemic action as it is not absorbed in sufficient amount; it is either destroyed in the gastro-intestinal tract or rapidly conjugated and oxidised in the liver. This substance is normally given subcutaneously or intramuscularly. Intravenous injection of standard preparations is highly dangerous as it is likely to precipitate *ventricular* fibrillation—a condition which is nearly always fatal in man.

PHARMACOLOGICAL ACTIONS. The response to adrenaline in man resembles that produced by stimulation of adrenergic nerves. The main actions are on the heart, blood vessels and smooth muscle. A minute amount of adrenaline given *experimentally* by the intravenous route produces a rise in blood pressure with increased heart-rate and cardiac output. When 0.5 mg. is injected subcutaneously the following effects are apparent. The heart rate is usually increased, the systolic pressure rises but the diastolic pressure falls, and as a result the pulse pressure increases. This effect on the diastolic blood pressure is most apparent in young adults with a healthy and resilient cardiovascular tree. The arterioles and capillaries of the skin and mucosæ are constricted, but the blood vessels of skeletal muscle and the coronary arteries are dilated. The bronchial muscle is relaxed and vascular congestion of the bronchial mucosa, if present, is decreased. This spasmolytic action on bronchial muscle is readily demonstrable when spasm is present as in asthma. The smooth muscle of the gastro-

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intestinal tract is relaxed and that of the pyloric and ileocaecal sphincters contracted. The detrusor muscle of the urinary bladder is relaxed and the trigone and sphincter contracted. The splenic capsule is contracted. Even this small dose (0.5 mg. subcutaneously) produces in some people a feeling of restlessness, with vague apprehension, tremor and headache. These symptoms and signs are common to the state of hyperadrenalinæmia and the "panic syndrome": many of the physical accompaniments of fear are produced by increased secretion of adrenaline. The "clinical picture" naturally has much in common with that seen in hypoglycæmia (often a direct effect of overdose with insulin) where there is rapid increase in the amount of circulating adrenaline—designed to increase glycogenolysis and raise the blood sugar. Again in thyrotoxicosis it is possible to identify some of the symptoms as the effects of excessive secretion of adrenaline—insomnia, restlessness, irritability and tremor.

Adrenaline has also important effects on metabolism: it accelerates the depletion of the glycogen depots in liver and skeletal muscle and thus produces a rise in the blood sugar and lactic acid content of the blood. The injection of adrenaline is therefore a logical method of treatment of the hypoglycæmia that follows overdosage with insulin. There is an important proviso: there must be adequate stores of glycogen in the liver and elsewhere, and as the stores are often depleted in the circumstances under consideration, the administration of glucose by the appropriate route is to be preferred. Adrenaline administration also produces a mild "stress" response and increases the release of corticotrophin. This results in a decrease in the eosinophil count in the blood and an increased urinary excretion of 17-ketosteroids. An injection of adrenaline has only a slight and transient stimulating effect on the cerebrum, and its action on the vital centres in the medulla is negligible.

*Methods of Administration.* Topical application of adrenaline solution to mucous membranes produces vasoconstriction. This blanching effect can also be seen when adrenaline is injected intradermally—as it is when procaine is being used as a local anæsthetic (p. 170). In order to produce systemic effects adrenaline

is given by subcutaneous or by intramuscular injection. Its absorption can be delayed and its action prolonged by suspending the adrenaline in oil. Strong solutions (1 per cent), nebulised and inhaled, have actions which are ordinarily restricted to the respiratory tract. If large amounts are inhaled or if average doses are taken too frequently, systemic effects may develop. The dose of Adrenaline Acid Tartrate for an adult is 0.2-0.5 ml. of a 1 in 1,000 solution by subcutaneous or intramuscular injection. As explained above, adrenaline is not given by mouth.

#### Therapeutic Uses

When it is used topically, the objective is to produce vasoconstriction and thus to control capillary bleeding. For this purpose a freshly prepared solution of 1 in 2,000 is used: it is often effective in controlling bleeding from gums, tooth cavities, nose or throat and can also be employed during surgical procedures to arrest capillary oozing in the operation field. A spray of adrenaline (strength 0.1 per cent in liquid paraffin as a "vehicle") can be used to relieve nasal congestion in such conditions as sinusitis or hay fever. In debilitated patients and in infants the instillation of medicated oils into the nose is not free from danger: if the patient is recumbent the oil is apt to trickle into the respiratory tract and gravitate to the bases of the lungs where it may set up a low-grade pneumonia.

Adrenaline is commonly added to solutions of certain local anaesthetics to limit and thus prolong the action by causing vasoconstriction. (p. 170). In Stokes-Adams syndrome associated with complete heart block (A-V dissociation), adrenaline may be of temporary value in aborting the syncopal attacks by increasing the ventricular rate. Adrenaline is also used as an intracardiac injection in resuscitation, e.g. in drowning and in anaesthetic collapse. Such treatment is classed among the desperate remedies. The presence of adrenaline in the myocardium may cause a resumption of normal cardiac contractions, but it may prove so powerful a stimulus that the heart may respond by developing ventricular fibrillation—a rhythm which is nearly always fatal in man. Some of the successes attributed to the injection of adrenaline into the myocardium have probably been due simply to the

physical stimulus of needle puncture. It must be emphasised that adrenaline should not be used in treating the sudden syncope following the administration of chloroform or cyclopropane as these anaesthetics sensitise the heart to adrenaline, and thus the injection may precipitate ventricular fibrillation.

The main therapeutic use of adrenaline is to relieve acute bronchiolar spasm in asthma. If used at the onset of symptoms, adrenaline—even a small dose—often produces prompt and even dramatic relief. Adrenaline Injection, 0.5 ml. is injected subcutaneously. If relief is not obtained the dose should be repeated after 15 minutes. Thereafter, smaller doses may be given (0.25 ml.) according to the response obtained in the individual patient. The use of adrenaline in the control of asthma illustrates an important general principle. The practitioner requires to know the pharmacological action of the drug so that he may practise therapeutics in a logical fashion. Not less important, however, is the need to acquire skill in using this knowledge to the best advantage; and such skill is often empirical—still awaiting scientific analysis. Thus an asthmatic who has been trained to use adrenaline at the first warning of the onset of a paroxysm often succeeds in aborting the attack and invalidism is reduced to a minimum. On the other hand procrastination in the use of adrenaline often results in “adrenaline resistance” so that relatively enormous doses fail to give adequate relief: the patient is completely incapacitated, and in the *status asthmaticus*, he constitutes a major medical emergency. Relief in asthma can also be obtained from oral inhalation of a 1 in 100 solution by atomiser, but better results from inhalation are obtained from Isoprenaline Spray which contains 1 per cent of the drug (p. 682).

The vasoconstrictor action of adrenaline has an important application in cases of urticaria (nettle rash). The lesions in the skin and mucous membranes are characterised by local vasodilatation, œdema, and burning and itching which may be intolerable. The subcutaneous injection of adrenaline solution (0.5 ml. followed if necessary by 0.25 ml. in half an hour) brings rapid relief. Treatment by means of antihistamines (p. 284) is usually given simultaneously in anticipation of further crops of urticarial lesions but it must be understood that the antihistamines do not



relieve *existing* lesions—which can be dealt with promptly by means of adrenaline and by a totally different pharmacological mechanism. When urticarial eruptions complicate other diseases, such as serum sickness and adverse reactions to the injection of organic arsenicals, the same approach to treatment should be adopted.

### NORADRENALINE

Noradrenaline differs chemically from adrenaline in the absence of a methyl radical in the terminal amino group and is sometimes described as “demethylated adrenaline”. Like adrenaline it is released at the endings of sympathetic postganglionic nerve fibres. It is also produced in the adrenal gland. Again it resembles adrenaline in that it is destroyed in the tissues by amine oxidase; and conjugated forms are excreted in the urine.

Pharmacologically noradrenaline shares with adrenaline the vasoconstrictor action on cutaneous blood vessels; but whereas adrenaline produces dilatation of vessels in skeletal muscle, noradrenaline causes constriction. There is an important contrast in the effects of these two substances on the blood pressure. Noradrenaline, by its action in producing widespread peripheral vasoconstriction causes a steady rise in both the systolic and the diastolic readings. Adrenaline, which does not increase the total peripheral resistance, results in a raised systolic pressure but the diastolic blood pressure is either unchanged or lowered. Adrenaline produces considerable tachycardia by a direct action upon the heart. On the other hand noradrenaline promptly causes slowing of the heart; this is a reflex effect following the rise in the systolic and diastolic blood pressures. Cardiac output is increased by adrenaline but not by noradrenaline. Compared with adrenaline, noradrenaline is a weak bronchodilator.

The therapeutic importance of noradrenaline lies in its action on systolic and diastolic blood pressure. It can be infused intravenously without causing adverse constitutional effects. By contrast, adrenaline given intravenously causes acute apprehension, tremor and palpitation: reference has been made to the danger of causing ventricular fibrillation in this way. In peripheral vasomotor collapse (shock, or overdose with ganglion-blocking agents)

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Noradrenaline Acid Tartrate is infused slowly intravenously. The drug is added to the perfusion fluid (physiological saline or dextrose solution). The quantity given depends upon the response of the individual patient. The range of dosage is 5-25 microgrammes *per minute* and the concentration of noradrenaline in the infusion should not exceed 8 microgrammes per ml. Further, when noradrenaline is used in the treatment of severe myocardial infarction, care is necessary because *in these patients* the drug may precipitate ventricular fibrillation (see adrenaline, p. 136).

**ISOPRENALINE SULPHATE.** This is a colourless crystalline powder soluble in water which darkens on exposure to light and air. Its effect in producing dilatation of the bronchi is much more powerful than that of adrenaline or noradrenaline. As it can be used without the inconvenience and discomfort of injection, it is of special value in the treatment of asthmatic attacks and is used sublingually in a tablet of 20 mg. A solution of 1 per cent isoprenaline sulphate administered by inhalation from an all-glass atomiser produces a more rapid effect. Not more than 1 ml. of solution should be used at a time. Overdosage may cause side-effects such as palpitation and precordial pain. This drug is contra-indicated in acute coronary disease and should not be administered at the same time as adrenaline.

## EPHEDRINE

Ephedrine is an alkaloid obtained from plants of the genus *Ephedra* most commonly found in China and northern India. These herbs, containing ephedrine and called *ma huang*, have been used empirically by Chinese physicians for over 5,000 years.

Ephedrine is the hemihydrate of (–)-2-methylamino-1-phenylpropanol and is related chemically to adrenaline. It seems likely that ephedrine acts by preventing the rapid destruction of adrenaline by amine oxidase and thus prolonging the action of the adrenaline liberated at the sympathetic nerve endings.

**PHARMACOLOGY.** Ephedrine is a potent sympathomimetic drug which produces peripherally responses simulating those ob-

tained by stimulating adrenergic nerves. It raises blood pressure, stimulates heart muscle, causes constriction of arterioles and relaxes the smooth muscle of the bronchi and the gastro-intestinal tract. The pupil dilates and the metabolic rate is increased. Ephedrine differs from adrenaline in being effective by mouth and as it is more stable it has a longer duration of action. Its effect on arterioles is less than that of adrenaline but it lacks the vasodilator component (in skeletal muscle)- which in the case of adrenaline causes a fall in diastolic pressure. Following the administration of ephedrine the heart rate is at first accelerated and later slowed by reflexes from the carotid sinus. Ephedrine stimulates the central nervous system; this action is of value in bronchial asthma as ephedrine not only produces relaxation of the bronchioles but it also stimulates the respiratory centre. Ephedrine increases the tone of the sphincter of the urinary bladder and this is the reason why the drug is used in nocturnal enuresis (bed wetting in children) and in urinary incontinence. It must be added that in these troublesome conditions ephedrine is of value in only a minority of cases. It is possible that in these patients the effect of ephedrine on the bladder sphincter is less important than the stimulating action on the brain- which prevents deep sleep and in this way diminishes the likelihood of incontinence.

*Absorption, Fate and Excretion.* Ephedrine is readily absorbed from the intestinal tract and also when given parenterally. It is excreted mainly unchanged by the kidney. Ephedrine Hydrochloride is usually given by mouth in a dose of 16-60 mg. but can be injected intramuscularly or with care intravenously. Local application of drops or sprays may be used on mucous membranes and watery or oily solutions of 0.5-2 per cent are employed.

*Side-effects.* Ephedrine also has a mydriatic action on local application and after systemic administration. Large doses induce headache, nervousness, insomnia and occasionally nausea and vomiting. Difficulty in micturition is not uncommon in older people and præcordial pain occurs occasionally. It should be used with caution in patients who have organic heart disease, hyperthyroidism, hypertension or angina pectoris.

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**THERAPEUTIC USES.** Ephedrine is widely used to prevent or to abort asthmatic paroxysms and it is sometimes valuable in the actual treatment of minor episodes. Ephedrine is of use in the symptomatic relief of hay fever and acute sinusitis: in these conditions it is applied locally.

One therapeutic application of ephedrine is in maintaining blood pressure during spinal anaesthesia and to combat postural hypotension. In the symptomatic treatment of complete heart-block with fainting attacks (Stokes-Adams syndrome) it has been of benefit.

Ephedrine can also be employed as a mydriatic: its action is of short duration, but as it causes only a slight increase in intra-ocular tension it is to be preferred to homatropine for diagnostic purposes in old people. A 3 per cent aqueous solution of the hydrochloride produces satisfactory dilatation of the pupil within 30 minutes.

Ephedrine can be used to stimulate the medullary centres in the treatment of poisoning by cerebral depressants such as morphine or barbiturates, but these symptomatic measures are less important than using the appropriate antidote (see nalorphine, p. 700, and bemegride, p. 691). Ephedrine is effective in combating narcolepsy.

The beneficial effect of neostigmine in myasthenia gravis can be intensified and prolonged by giving ephedrine. It is also of some value in relieving the paroxysms of whooping cough. Good results occasionally follow in the treatment of nocturnal enuresis and urinary incontinence, but in these cases insomnia may be a side-effect. Some people are excessively sensitive to the stimulating action of ephedrine and are made wakeful and nervous. It is wise therefore to order the last dose to be given before 4 p.m. so that this side-effect may be avoided.

### AMPHETAMINE

This substance, introduced as "Benzedrine", is closely related to ephedrine in chemical structure. It is a colourless liquid which volatilises slowly with a faint odour resembling the smell of geranium leaves. The preparation most commonly used is the sulphate— a white bitter-tasting powder, available for use in the form of tablets. Amphetamine is rapidly absorbed from the ali-

mentary tract and is partly inactivated in the liver and partly excreted unchanged in the urine.

Amphetamine is a sympathomimetic amine, but it has only a weak action on the peripheral part of the autonomic nervous system. It is a powerful cerebral stimulant and this action accounts for its therapeutic applications. If large doses are given the sympathomimetic effects can be elicited including pallor, dilatation of the pupils, a spasmolytic effect on the bronchioles in asthma, and some increase in the blood pressure, but amphetamine is rarely the drug of choice for producing such effects in clinical practice, because the stimulating action of the drug on the cerebral cortex and on the medullary centres, *when sustained*, may ordinarily be regarded as very undesirable side-effects.

Amphetamine is a powerful stimulant of the respiratory centre and it counteracts the central depressant effects of hypnotic and anæsthetic drugs. A large dose of amphetamine (10 mg. or more) by mouth causes cerebral stimulation and the effects are easily recognised by the normal person in terms of alteration of the psyche: there is often a temporary increase in alertness, greater self-confidence and an increased capacity for sustained intellectual work. Shapening of the imagination produces more intense concentration and a desire to make the greatest intellectual effort. This enhanced intellectual tone characterised by freedom from fatigue resembles the well-known caffeine effect in an exaggerated form. Although there is greater interest in work and often greater drive, the quality of the performance cannot be predicted with certainty: it varies from one person to another and may even vary in the same individual under different conditions. At the extremes there are those who achieve an increased output of accurate work which is entirely acceptable; there are others who—though not obviously excited—become erratic in their thinking and their efficiency is correspondingly impaired. These apparently contrasting effects are perhaps to be explained by recalling a general principle which is of great importance to the medical practitioner concerned with pharmacology: the effect of a drug is determined not only by its intrinsic properties, but to a very large extent by the state of the tissues on which it acts, and often by the “physiological climate” at the time of administration. Thus am-

phetamine cannot *create* intellectual power, but it may release it; the drug can act to the best advantage on the higher centres of the brain only when these are histologically normal, and when the mental processes have been disciplined by adherence to a well-designed plan of education. Another important general principle is that even in the most favourable circumstances the stimulating action of amphetamine cannot be maintained indefinitely. Further, the nature of the action of amphetamine even on the individual is difficult to predict; and on a large group of people who are together undertaking a task (e.g. soldiers engaged on a military operation), it is impossible to foresee the outcome. Susceptibility to the cerebral effects of the drug vary considerably: many people are subjectively affected by a dose as small as 1 mg. whereas others can take ten times this dose with negligible effects. It follows that although there may be occasions when such exploitation of activity may be justified, they are rare. The temporary flare-up is followed by relative inactivity or even exhaustion; a store of intellectual power intended for a day's ordinary work is consumed in a few hours.

*Toxic Effects.* In clinical practice side-effects commonly seen include headache, palpitation, agitation and, occasionally, mental confusion. After large doses mental depression occurs almost invariably. In serious overdosage, restlessness, tremor, delirium with palpitation, angina and circulatory collapse may occur. Amphetamine produces dilatation of the pupil when a solution is instilled into the conjunctival sac, but not usually after systemic administration. It does not cause a rise in intra-ocular pressure or paralyse accommodation, and the pupil returns to normal size sooner than it does after homatropine. As with ephedrine, the sphincter muscle of the bladder contracts and the detrusor muscle relaxes after amphetamine, but this action is of academic interest; the cerebral effects of the drug prohibit its therapeutic use in cases of nocturnal enuresis.

Amphetamine and dextro-amphetamine reduce appetite and thus diminish food intake. This important action appears to be the outcome of enhanced mental activity: it would appear that interest in intellectual exercises renders the patient temporarily indifferent to the pleasures of eating.

Amphetamine was formerly widely used as an inhalant to relieve nasal congestion. The action is attributable to vasoconstriction the outcome of a sympathomimetic action in the nasal mucous membrane. This is undoubtedly an effective way of relieving the discomforts of nasal obstruction. However it is open to serious doubt whether these vascular effects on inflamed tissues are desirable; ischaemia may well predispose to secondary infection. Further, repeated use of inhalations of amphetamine produces the cerebral effects with the risk of insomnia; and occasionally such patients become addicted to the drug. The use of amphetamine in inhalers has therefore been discouraged. Addiction tends to be found in those who experience euphoria after the drug; its repeated use promotes a condition of chronic restlessness and hyperexcitability alternating with depression and even melancholia. Repeated use of amphetamine may produce sympathomimetic effects in the alimentary tract with flatulent distension and erratic bowel rhythm. Dependence on the drug is not usually so great that there is much difficulty in breaking the habit.

In the treatment of narcolepsy doses of 5-10 mg. several times daily usually give relief. Amphetamine is also useful in diminishing rigidity and abolishing the oculogyric crises sometimes seen in postencephalitic Parkinsonism. In this condition the drug is usually employed to supplement other treatment—such as a course of atropine or stramonium (p. 124).

Amphetamine was formerly used also as an analeptic in the treatment of barbiturate poisoning (p. 215). The commonest use of amphetamine and dextro-amphetamine now is to help excessively fat people to adhere strictly to a regimen of reduced diet (see above): the justification for this practice is discussed in textbooks of therapeutics. The drug has also been used in the treatment of orthostatic hypotension. Reference has been made to the rationale for prescribing it in nocturnal enuresis of children, in the nasal congestion of hay fever, or for the acute rhinitis of the common cold.

## SYNTHETIC PREPARATIONS WITH SYMPATHOMIMETIC ACTIONS

A very large number of sympathomimetic amines have been produced by synthetic chemists. The objective is to synthesise a pressor substance which approximates to the ideal. Such a compound is one which has a prompt and powerful effect achieved by selective action on the sympathetic control of peripheral vessels, maintains the blood pressure at physiological levels for several hours, has no direct action on the heart, is not a cerebral stimulant, and does not exhibit the phenomenon of tachyphylaxis (diminishing response to a series of doses). The circumstances in which these substances are employed therapeutically make it imperative to use the parenteral route of administration. Although ranges of dosage are mentioned for each drug, it must be emphasised that these figures offer only general guidance: the "correct" dose is that which produces the desired effect in the individual patient and in the existing circumstances. When these pressor amines are given intravenously, they are infused *slowly*—taking fully two minutes—so that the effects can be checked at quarter-minute intervals. Many of these drugs can be given intramuscularly. The relative merits of intravenous and intramuscular administration are mentioned elsewhere (p. 13): there are often advantages in giving a small dose intravenously for its immediate action and a larger dose intramuscularly to ensure a more sustained effect. A few preparations are selected for brief comment.

*Cyclopentamine hydrochloride* ("Clopane Hydrochloride") has pressor effects similar to those of ephedrine. It can be used for maintaining blood pressure during spinal anaesthesia. Its advantage over ephedrine lies in the fact that it produces only slight cerebral stimulation. It is used in a dose of 10 mg. by slow intravenous injection or by giving 25 mg. intramuscularly. As a nasal decongestant it is applied locally as 0.5-1 per cent solution in normal saline.

*Hydroxyamphetamine Hydrobromide* ("Paredrinex"). Although the pressor effect of hydroxyamphetamine is twice as great as that



of ephedrine, cerebral stimulation is negligible. It is therefore used therapeutically only for its action on blood vessels. A 1 per cent solution applied to a congested nasal mucous membrane, causes shrinkage and ischaemia. If instilled into the eye (2 per cent solution) it produces dilatation of the pupil lasting for about 2 hours; and for this purpose, it is sometimes combined with 4 per cent homatropine hydrobromide solution (one drop) in order to intensify the effect.

*Mephentermine sulphate.* This compound, which is also known as Mephedrine sulphate, is Trimethylphenethylamine sulphate dihydrate. Its sympathomimetic effects are similar to those of ephedrine and amphetamine. It causes peripheral vasoconstriction and increases the blood-pressure. It has no direct action on the heart. Mephentermine stimulates the central nervous system but this action is much weaker than that of amphetamine. It is used therapeutically to maintain blood pressure in hypotensive states, for example, following surgical operations, during spinal anaesthesia and in the treatment of myocardial infarction. Although the immediate effects in correcting hypotension are satisfactory, they tend to diminish with repeated administration: this is the phenomenon of tachyphylaxis. If given intravenously, the injection is made *slowly*: up to 50 mg. may be needed. The dose by intramuscular injection is 15-30 mg. Mephentermine can also be applied locally as an aqueous solution (0.5 per cent) for the relief of nasal congestion in acute rhinitis.

*Methoxamine hydrochloride* has a sustained pressor action, and its side-effects are so few that it approximates fairly closely to the ideal. It has no direct action on the heart, but when the arterial blood pressure rises there may be bradycardia of reflex origin; it is not a cerebral stimulant; it has no action on the bronchioles. Peripheral vasoconstriction is accompanied by a pilomotor action. This preparation is employed parenterally to maintain or restore blood pressure during operative procedures, spinal anaesthesia and in the management of myocardial infarction. It is noteworthy that methoxamine hydrochloride can be safely used to raise blood pressure during cyclopropane anaesthesia. The intravenous dose is 5-10 mg.: by intramuscular injection a slightly larger dose may be given—10-15 mg.

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*Methoxyphenamine hydrochloride.* By contrast with the preceding preparations, methoxyphenamine hydrochloride is remarkable for its sympathomimetic action on the bronchial tree and its negligible effect on the cardiovascular system. It is therefore used as an alternative to ephedrine in the prevention of paroxysms of asthma; and it can be used to combat allergic rhinitis and urticaria where it is particularly desirable to avoid the cardiovascular side-effects of more powerful adrenaline-like substances. As a preventive in asthma the dose is 50-100 mg.

*Methylamphetamine Hydrochloride* is a white, odourless, crystalline powder with actions similar to those of amphetamine. In solution it is used mainly by inhalation for relief of congestion of nasal mucosa. The hydrochloride is a white crystalline powder. Its action is more rapid than that of amphetamine sulphate, and it lasts for a longer time. Methylamphétamine hydrochloride is a slightly more powerful cerebral stimulant with less prominent circulatory effects. It is given intravenously to restore blood-pressure during spinal anaesthesia, in postoperative shock and in overdosage with morphine or the barbiturates. The intravenous dose is 10-30 mg.

*Naphazoline Hydrochloride.* By contrast with other sympathomimetic amines this preparation produces *depression* of the higher centres. Peripherally it acts mainly as a powerful vasoconstrictor and is accordingly used for the relief of nasal congestion as a local application in 1 in 2,000 aqueous isotonic saline.

*Phenylephrine Hydrochloride.* This amine resembles adrenaline in its chemical structure. Its actions are mainly on the cardiovascular system: it produces a rise in blood-pressure which is sustained and accompanied by reflex bradycardia. The dose is 5 mg. subcutaneously or 150 mg. orally. There is also peripheral vasoconstriction and this warrants its topical use for the relief of congested mucosæ. Instilled into the eye it causes dilatation of the pupil but there is no interference with accommodation. Phenylephrine is used to sustain the blood pressure during spinal anaesthesia and in the treatment of myocardial infarction. Locally it is of value in rhinitis and sinusitis as a decongestant, and its mydriatic effect is applied in ophthalmology for diagnostic work. It has also been given intravenously in a dose of 0.5 mg. to correct

supraventricular paroxysmal tachycardia and to restore normal sinus rhythm.

*Phenylpropanolamine Hydrochloride* (Norephedrine: "Mydriatin"). The chemical relationship between this compound and ephedrine is noteworthy. Its actions are very similar to those of ephedrine - both centrally and on the autonomic nervous system. It is used locally as a vasoconstrictor for congested mucous membranes and as a 1 per cent solution in saline - as a spray or by instillation. It has also been given in asthma but it is not the most suitable of the sympathomimetic amines (25 mg. capsules orally every 4 hours).

*Methyl Phenidate Hydrochloride* ("Ritalin") is a soluble crystalline powder. It has a central nervous stimulant action resembling that of amphetamine. Methyl phenidate hydrochloride, however is not a sympathomimetic amine. It has a limited application in the treatment of depressive states and may be of ancillary value in the management of lassitude and apathy following severe illness. The usual dose is 10-20 mg. by mouth once or twice daily. In order to avoid causing insomnia the last dose should be given not later than 4 p.m.

*Pipradol Hydrochloride* ("Meratran"). This is a white crystalline powder. It does not act as a sympathomimetic amine and yet its effects closely resemble those of amphetamine. It has a much weaker action than amphetamine, but there is a well-defined action on higher centres of the brain with increased mental activity. There is an appreciable improvement in mood and the sense of fatigue is relieved. Compared with amphetamine there is less tendency to depression after the phase of stimulation, but this may be attributable to the relatively weak stimulation of sub-cortical zones in the prefrontal region. It has been recommended in elderly people and is used in a dose of 1-2 mg. by mouth three times per day.

*Phenmetrazine* ("Preludin") is 3-methyl-2-phenylmorpholine. Qualitatively it resembles amphetamine in its pharmacological action. There is said to be an important bias, however, towards diminution of appetite and only minimal sympathomimetic action, but this claim is *sub judice*. Toxic effects (psychoses) have been reported from gross overdose. It must be remembered that

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patients who use this and other "anorexic agents" are not infrequently unstable psychologically, and their treatment—in all its aspects—demands particularly careful supervision. It is given by mouth in a dose of 25 mg. twice or three times per day about 30 minutes before a meal.

## ADRENOLYTIC DRUGS

These drugs inhibit the responses of effector cells to adrenergic sympathetic nerve impulses and to adrenaline. They are of much greater interest to the pharmacologist than to the physician, as so far they have not found an important place in therapeutics. In general these substances antagonise the *motor effects* of adrenaline and of the sympathetic system more readily than the inhibitory actions. The classic example is that adrenaline administered after ergotoxine, an adrenolytic, causes a fall in blood pressure. The adrenolytic drugs usually lower the blood pressure and dilate the peripheral vessels but have no effect on the smooth muscle of the gut. Miosis may follow their administration; and lowering of intra-ocular tension may occur, but only when it is raised. Their main use in clinical practice is in the investigation of suspected cases of pheochromocytoma. This is a somewhat rare hyperfunctioning tumour of the adrenal medulla composed of chromaffin tissue and usually of benign adenomatous nature, but liable to exhibit overactivity. Very large quantities of adrenaline and noradrenaline are discharged from these into the blood, and paroxysmal hypertension develops with pallor, sweating and apprehension. As a sudden fall in blood pressure occurs in this disease after giving adrenolytic drugs, the procedure is clearly valuable in diagnosis. They are also useful in controlling the blood pressure prior to operation and while handling the tumour at the time of operation. The skilful use of adrenolytic drugs prevents sudden paroxysms of gross hypertension.

A more common but less satisfactory therapeutic application is in the treatment of peripheral vascular disease such as Raynaud's disease, arteriosclerotic vascular occlusion and narrowing. Occasionally relief of malignant hypertension has followed the use of these substances and they have also been employed in the

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treatment of glaucoma. The ergot derivatives have been of particular value in the relief of migraine. Many different chemical compounds have adrenolytic properties, and the first group to be considered is the  $\beta$ -haloalkylamines. These substances are closely related to the nitrogen mustards.

*Dibenamine* and *dibenyline* are both  $\beta$ -halo-alkylamines and although dibenamine was the first compound of this class to be found with an adrenolytic action, it has no application in present-day therapeutics.

### DIBENYLINE

This is a powerful adrenolytic substance given by mouth in doses of 10 mg. in capsules. It has a long duration of action. It is used in a dose of 1 mg. per Kg. body weight intravenously in suspected cases of pheochromocytoma to reduce the blood pressure. It has been stated that the prevention by this substance of pressor responses to histamine is the most specific pharmacological test for such tumours. By mouth in 20-200 mg. daily dosage it finds therapeutic application in the pre-operative management of patients with pheochrome tumours.

### ERGOT ALKALOIDS

Many alkaloids of ergot including ergotoxine, ergotamine, dihydroergotamine, dihydroergocornine, dihydroergocristine and dihydroergocryptine have adrenolytic properties. Ergotamine tartrate in a dose of 0.25 mg. subcutaneously or 1-2 mg. by mouth is used for the relief of migraine. Dihydroergotamine in 1 mg. dose subcutaneously is also of value in this condition. "Hydergine", a proprietary mixture of equal parts of the methanesulphonates of dihydroergocornine, dihydroergocristine and dihydroergocryptine, is employed in the treatment of peripheral vascular disease and is given in a dose of up to 0.75-1.5 mg. orally or 0.3 mg. by intramuscular injection. Imidazoline compounds—tolazoline and phentolamine are also adrenergic blocking agents.

### TOLAZOLINE HYDROCHLORIDE

This substance has moderate adrenergic blocking actions but has in addition numerous other effects. Like the sympathomimetic

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drugs it causes increased force of contractions of the heart and also coronary vasodilatation. However, it also has other important effects: some are parasympathomimetic, namely stimulation of intestinal activity, and others are histamine-like actions including vasodilatation and stimulation of gastric secretion.

Tolazoline has little effect on the blood pressure, but it causes appreciable dilatation of peripheral blood vessels—especially of arterioles and capillaries; thus it increases peripheral blood flow. Side-effects consist in flushing of the skin, apprehension and palpitation. Large doses cause nausea and vomiting.

Tolazoline Hydrochloride is used in peripheral vascular disease to relax arterial spasm, increase blood flow and relieve pain. It is given by mouth in a dose of 25–50 mg. three to four times per day. It is reported to relieve the muscle pain and spasm of anterior poliomyelitis in the acute stage of the disease. This substance has also been employed in the treatment of conditions resulting from peripheral arteriosclerotic occlusion such as leg ulcers and impending gangrene. In these conditions the best results are obtained by the rapid intra-arterial injection of 10–50 mg. Tolazoline can be used as a substitute for histamine in testing gastric function in a dose of 10 mg. intramuscularly. Intravenous injections of 50 mg. have also been tried in the treatment of occlusion of the central retinal artery and in toxic amblyopia.

### PHENTOLAMINE HYDROCHLORIDE

This drug has greater adrenolytic effects than has tolazoline and blocks the pressor action of adrenaline. It is used in the diagnosis and pre-operative treatment of patients with pheochromocytomas and in peripheral vascular disease. Side-effects are nausea, vomiting, tachycardia and orthostatic hypotension. It is given orally as the hydrochloride in doses of 50–100 mg. four to six times per day.

The methanesulphonate is the preparation recommended for intramuscular or intravenous injection. An intravenous injection of 5 mg. is used as a standard test for pheochromocytoma and should produce a fall in blood pressure of 35 mm. Hg. in the systolic and 25 mm. Hg. in the diastolic. It is stated to produce more false positives than does piperhexane.

## PIPEROXANE HYDROCHLORIDE

Piperoxane Hydrochloride, a benzodioxane, has a transient adrenergic blocking effect but has many other actions. It stimulates the smooth muscle of the peripheral and coronary blood vessels, uterus, gastro-intestinal tract and bronchi. It has also a depressant action in the myocardium. The only clinical use of this substance is in the diagnosis of phaeochromocytomas. An intravenous injection of 0.25 mg. per Kg. of body weight (maximum dose 20 mg.) is given in 3-5 minutes and its action lasts 10-30 minutes. It is not a very safe drug as it tends to raise the blood pressure in patients with essential or malignant hypertension, possibly by stimulating the sympathetic centre in the brain. The side-effects include headache, a metallic taste in the mouth, nausea, palpitation, flushing, sweating and apprehension.

## AZAPETINE PHOSPHATE

This is a weak adrenolytic substance with similar actions to tolazoline. It is given by mouth in a dose of 25-75 mg. and used in peripheral vascular disease.

*Yohimbine Alkaloids.* The alkaloids derived from a West African yohimbe tree have adrenolytic actions, but yohimbine and similar substances have not yet been shown to have therapeutic value.

## GANGLIONIC BLOCKING AGENTS

Many drugs can be shown by suitable pharmacological techniques to impair transmission in ganglia of the autonomic nervous system, that is to say they are ganglion-blocking agents. Some of these, such as certain general anaesthetics and barbiturates, have powerful actions on the central nervous system and the ganglion-blocking effect is not clinically important. Others, of which nicotine is the classic example (p. 110), have an initial stimulant action before the blocking action becomes apparent. Nicotine also has similar effects at the neuromuscular junction and upon cells of the central nervous system. These widespread

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actions prohibit its use in therapeutics as a ganglion-blocking agent. A further group, however, of which hexamethonium may be taken as the prototype, have virtually no pharmacological actions other than the production of ganglionic blockade, and these drugs are used principally in the treatment of arterial hypertension. Hexamethonium has been studied in greater detail than any of the other members of the group and its actions will be described at some length. Reference is also made to other remedies which have been shown to be clinically useful.

**CHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIPS.** The greater number of ganglionic blocking agents possess, in common with acetylcholine, a quaternary ammonium group. The simplest compound in which the blocking activity (without preliminary stimulation) is highly developed is tetraethylammonium in which four ethyl groups replace the hydrogen atoms in the ammonium group. This compound, as the bromide, has been used in therapeutics and as a "pharmacological tool" and is briefly described later in this section. The corresponding methyl derivative—tetramethylammonium—is a ganglionic stimulant not used in therapeutics. When the nitrogen atoms of two trimethylammonium groups are linked by a chain of methylene groups a series of highly active compounds—the polymethylene bis-trimethylammonium or methonium compounds—is obtained. The type of pharmacological activity depends upon the length of the inter-nitrogen bridge and the individual members of the series are designated by the Greek prefix denoting the number of carbon atoms in the polymethylene bridge. Thus pentamethonium ("C<sub>5</sub>") and hexamethonium ("C<sub>6</sub>") are potent ganglion-blocking agents and decamethonium ("C<sub>10</sub>") is described later (p. 237) as a neuromuscular blocking drug. The quaternary nitrogen may be included in a ring structure as in pentolinium, and other atoms may replace carbon atoms in the interjacency as for example in pentacynium. In the complex chemical structure of trimetaphan a sulphur atom replaces the quaternary nitrogen. More recently compounds have been developed without quaternary nitrogen groups in which ganglion-blocking activity is well-developed, for example mecamlamine and pempidine. In general these chemical



manipulations have not altered the fundamental pharmacological actions, but they have resulted in the production of drugs more suitable than the original compounds for long-term clinical use.

**MODE OF ACTION.** This has been studied in greatest detail in the case of TEA and hexamethonium. These drugs block transmission in autonomic ganglia by a selective action on the post-synaptic membrane. Conduction in preganglionic and post-ganglionic nerve fibres is not altered, nor is the release of acetylcholine at preganglionic nerve endings prevented. There is no initial stimulation of the ganglion cell (such as occurs with nicotine) and the cell is not depolarised by these drugs. The blockade results solely from elevation of the threshold of the ganglion cell to acetylcholine produced at preganglionic nerve endings. They are said to stabilise the postsynaptic membrane. Under the influence of ganglion-blocking agents of this type the effector cells innervated by postganglionic nerve fibres remain sensitive to specific mediators or direct stimulation. It is believed that active groups in the blocking drug become attached to receptor sites upon the ganglion-cell membrane, thereby denying access to acetylcholine which normally becomes attached to these sites with resulting depolarisation of the ganglion cell. It may be mentioned that while all autonomic ganglia are blocked in the manner described, not all ganglia are equally sensitive to the effects of these drugs. This observation makes it possible that drugs may yet be discovered with highly selective actions on a particular group of ganglia.

#### EFFECTS OF HEXAMETHONIUM IN MAN

**CARDIOVASCULAR SYSTEM.** Hexamethonium leads to reduction in arterial blood pressure and this action constitutes its most important therapeutic application. In a *normal* person in the recumbent posture the drug produces very little change in blood pressure, but in a patient with *arterial hypertension* a moderate reduction may be noted. In both cases postural hypotension usually develops when the person stands, and this may lead to giddiness and even syncope from cerebral ischaemia. There is considerable individual variation in the intensity of this effect, and postural hypotension induced by standing tends to be greater

in hypertensive subjects and in older people than in normotensive younger persons. The effect is increased by any other measures which tend to lower the blood pressure—for example other hypotensive agents or when there is sodium depletion. In hypertensive subjects postural hypotension may still occur when the blood pressure (taken while the patient is supine) has returned to its original level. The mechanisms involved in hexamethonium induced hypotension are probably as follows. Any reduction which occurs in the recumbent posture can be accounted for by a reduction in the total peripheral vascular resistance; the cardiac output and heart rate are not significantly altered. In the upright posture the marked fall in blood pressure is due to a sharp reduction in the cardiac output occasioned by a diminished venous return to the right heart. The diminished venous return is attributable to pooling of blood in the peripheral circulation under the influence of gravity, and the pooled blood is accommodated mainly in the veins. When the patient lies down the venous return is facilitated and the blood pressure rises. The compensatory vascular adjustments which prevent postural hypotension in the normal person are dependent upon an intact sympathetic vasoconstrictor outflow. Ganglionic blockade abolishes these vasoconstrictor reflexes at sympathetic ganglia level and there is thus no means of compensating for the effects of gravity upon the circulation. Overdosage with hexamethonium may produce severe hypotension with loss of consciousness from cerebral anoxia.

In patients with congestive heart failure, by reducing venous tone, hexamethonium lowers the central venous pressure and raises the cardiac output towards normal, thus acting in a similar manner to venesection. By reducing the raised peripheral resistance less ventricular work is required and these actions account for the dramatic improvement which may be seen in hypertensive heart failure. The blood flow through the various vascular beds is not equally affected by hexamethonium. Skin blood flow is generally increased, particularly in the feet and face which become warmer and flushed, but the hands are affected to a lesser degree. Muscle blood flow increases only moderately and the splanchnic blood flow is reduced during the hypotensive trough. The renal blood flow is also reduced in hypertensive subjects in

the upright posture, but it tends to recover spontaneously despite continued hypotension. Occasionally in hypertensive subjects in the recumbent posture the renal blood flow may increase even though a moderate fall in blood pressure occurs. The cerebral blood flow is well maintained unless the blood pressure falls precipitously. Patients with cerebral vascular disease may experience symptoms of cerebral ischæmia even with a moderate reduction in blood pressure, presumably because the rigid vessels cannot relax in the face of a falling perfusion pressure. The coronary blood flow behaves in a similar manner.

**OTHER SYSTEMS.** The effects of hexamethonium upon other systems are of little therapeutic value but constitute troublesome side-effects when the drug is used in the treatment of arterial hypertension. They are all due to autonomic ganglion blockade. The mouth becomes dry from a failure of salivary secretion and the volume and acidity of the gastric juice are decreased. Motor activity of the gastro-intestinal tract is inhibited with delayed gastric emptying and constipation. Severe ileus may occur, particularly if large doses of hexamethonium are given by mouth. The enhanced effect upon the gut when the drug is taken orally has been attributed to high concentrations within the lumen of the bowel, allowing direct access of the drug to parasympathetic ganglia in the wall of the gut. The pupil is dilated, the secretion of tears inhibited and there is difficulty in accommodation. Sweating is abolished, sympatho-adrenal discharge inhibited and the patient may be rendered impotent. Finally the action upon the bladder may produce difficulty in voiding urine or even cause complete retention. Measures to combat these side-effects are mentioned on p. 163. Enormous doses of hexamethonium produce neuromuscular blockade, but this does not occur within the therapeutic range of dosage.

*Absorption, Fate and Excretion.* Hexamethonium is poorly absorbed from the alimentary tract and the amount absorbed varies from person to person and in the same person from day to day. Usually not more than 5 per cent of the ingested dose is absorbed. After subcutaneous or intramuscular injection it is

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well absorbed and peak plasma levels are obtained within 1 hour. The drug is distributed in the extracellular fluid and is excreted unchanged in the urine by glomerular filtration. In patients with normal renal function, the greater part of the parenterally administered dose is excreted in a few hours and excretion is completed in 24 hours.

*Preparations, Administration and Dosage.* The official preparation is Hexamethonium Tartrate prescribed as the Injection or as Tablets. It contains 40 per cent of hexamethonium cation. The halides have also been used and the bromide is available commercially as tablets and as a solution for injection in various strengths. Because of the unpredictable absorption of hexamethonium from the gut most physicians no longer employ the oral route of administration. Bromism was also liable to occur when large doses of the salt were given by mouth. The subcutaneous route is usually chosen and intelligent patients may be taught to give the injection themselves once the dosage has been stabilised. The initial dose is 15-25 mg. given at 4-6-hourly intervals as determined by frequent measurement of the blood pressure in the supine and erect postures. The response varies from patient to patient and the dose and frequency of administration can only be determined by careful observation. The aim is to lower the blood pressure toward normal, short of producing symptoms of cerebral ischaemia. *Tolerance* to the action of the drug on the blood pressure develops during the early stages of treatment, necessitating a progressive increase in the single dose used in order to maintain the hypotensive action. It is of interest that tolerance does not develop to the actions of the drug upon the eye, secretions, or intestinal motility. The precise reason for this selectivity of action is not known, but it may be due to excessive sensitivity of arterioles and veins to the vasoconstrictor action of endogenous catechol amines. Hexamethonium may also be given intravenously but its brief duration of action makes this route of administration suitable only for the emergency treatment of hypertensive crises.

*Therapeutic Uses.* Hexamethonium is used mainly in the treatment of severe arterial hypertension. Patients are encouraged to

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be up and about so that the effect of the upright posture in reducing the blood pressure can be utilised. The place of ganglion-blocking drugs in the management of this condition is briefly discussed later in this chapter. Hexamethonium has also received clinical trial in peptic ulcer, acute pancreatitis and peripheral vascular disease but it is of doubtful value in these conditions.

### OTHER GANGLION-BLOCKING DRUGS

*Pentamethonium* ("C5") has the same actions as hexamethonium and is of similar potency. It has no advantages over hexamethonium and is no longer employed in therapeutics.

**TETRAETHYLAMMONIUM (TEA).** This compound is of historic interest as its main pharmacological properties were defined as long ago as 1914, but it has few therapeutic applications. It is a short-acting ganglionic blocking agent of competitive type. In man its effect upon the blood pressure is somewhat unpredictable, and in addition to the results of ganglionic blockade it may also cause paræsthesia, muscular twitching and muscular paresis. It also has a weak analgesic action, and in patients with phæochromocytoma a marked pressor response may result from intravenous injection of the drug. This last effect is thought to be due to direct stimulation of the tumour cells. It has been used as a diagnostic agent in hypertensive patients with suspected phæochrome tumour but histamine is more often employed for this purpose. Otherwise it has been replaced by hexamethonium and other ganglion-blocking drugs.

**PENTOLINIUM** acts as a ganglion-blocking drug in the same way as hexamethonium but weight for weight it is about five times as powerful in reducing blood pressure. It is more readily absorbed from the gastro-intestinal tract, about 30 per cent of the dose being excreted in the urine compared with 5 per cent of hexamethonium. Its maximal hypotensive effect occurs about 2-3 hours after oral administration and the action persists for 8-12 hours. Tolerance develops to the hypotensive action, but this is less marked than with hexamethonium and there is cross-

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tolerance with the latter drug. The side-effects are qualitatively the same as with hexamethonium, but it is less likely to produce severe constipation; impotence may be especially troublesome. The official preparation is Pentolinium Tartrate and it is dispensed as Tablets for oral use and as an Injection for subcutaneous administration. Tablets containing 10, 40 or 200 mg. are available and a solution (0.5 or 2.5 per cent) is usually employed for parenteral injection. Pentolinium is commonly given by mouth at 8- or 12-hourly intervals: the first dose is 20 mg. and this is raised by increments of 20 mg. until a satisfactory response is obtained. The frequency of administration and the total daily dose vary from one patient to another and often demand critical assessment. Subcutaneous administration may be used if oral therapy proves unsatisfactory. In these circumstances the dose must be appropriately reduced: the initial dose should not exceed 2.5 mg. Pentolinium is used in the treatment of severe hypertension. It has also been used in Pink Disease and to produce "controlled hypotension" during surgical operations.

**CHLORISONDAMINE.** The pharmacological properties of this asymmetrical bisquaternary compound are similar to those of pentolinium, but it is approximately twice as potent and its duration of action is longer. It is poorly absorbed from the gut, but a consistent effect may be obtained by oral administration twice or three times daily. It is available commercially as tablets containing 25 mg. or 50 mg. of chlorisondamine chloride and as a 2 per cent solution (5 mg. of the drug in an ampoule).

**PENTACYNIMUM** and other closely related drugs are long-acting ganglion-blocking agents. They have received clinical trial in severe hypertension but their clinical usefulness has not yet been fully assessed.

**TRIMETAPHAN CAMPHORSULPHONATE.** This complex thio-  
phanium derivative is a short-acting ganglionic blocking agent, but it also releases histamine and has a direct vasodilator action. These actions reduce blood pressure by lowering the total peripheral resistance and cardiac output. Its fate in the body is

unknown, but its transient action suggests that it is rapidly degraded. It is dispensed for use in vials containing 250 mg. of the drug and it is administered by intravenous infusion as a 1 in 1,000 solution; the rate of flow is adjusted to maintain the desired degree of hypotension. When the infusion is discontinued the blood pressure generally rises substantially within 10 minutes. Trimetaphan is used only to produce a degree of hypotension calculated to reduce bleeding in surgical procedures, especially in neurosurgery and in certain types of vascular surgery. When the systolic blood pressure is reduced to 60-80 mm. of mercury the blood flow and hydrostatic pressure in the raised part of the body are diminished and bleeding is thereby greatly lessened. The surgeon is thus presented with a relatively dry operation field. A number of complications such as vascular thrombosis, anuria, reactionary bleeding and shock have followed the use of trimetaphan and it is desirable that these techniques should be employed only by surgical teams skilled in their use.

**MECAMYLAMINE.** This compound described chemically as 3-methylaminoisocamphane is a secondary amine and does not possess a quaternary nitrogen group. As well as its ganglion-blocking properties, experimental evidence suggests that it has a direct depressant action upon heart muscle and on the smooth muscle of the gut. It is also a local anaesthetic and a neuromuscular blocking agent. The finer details of its pharmacological action have not yet been fully defined but it has been shown to act in a different manner to the quaternary ammonium compounds. Mecamylamine readily penetrates cells and it appears to alter the physiological state of the ganglion cell and muscle fibre so that their response to acetylcholine is modified. Of the side-effects common to all ganglionic blocking agents constipation is particularly severe with mecamylamine. Additional side-effects which have not been noted with the quaternary compounds include a coarse tremor, psychosis, and malaise or a persistent sense of "lack of well-being".

*Absorption, Fate and Excretion.* Mecamylamine is freely absorbed from the gut. It circulates partly bound to plasma protein, pene-

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trates readily into cells and crosses the blood-brain barrier. In all these respects it differs from the quaternary ammonium compounds. It is excreted unchanged in the urine and the rate of clearance is slow. Not more than 50 per cent of the dose is excreted during the first 12 hours after administration. If the urine is alkaline excretion is greatly reduced with a consequent prolongation of the intensity and duration of action.

*Preparations, Administration and Dosage.* Mecamylamine is used as the Hydrochloride available as tablets containing 2.5 mg. and 10 mg. It is given by mouth. The initial dose is 2.5 mg. twice daily, and the dose is increased by 2.5 mg. increments every 2-3 days until the desired response is obtained. Tolerance to its action is not a problem and there is no cross-tolerance to quaternary blocking agents. The effective dose varies greatly in different patients, but a fairly consistent effect can be obtained from day to day in the same patient.

*Uses.* Mecamylamine is used as an oral hypotensive agent in the treatment of severe hypertension; its main advantage over the older blocking drugs is its complete absorption which makes for a smooth and predictable hypotensive action.

**PEMPIDINE.** This newer ganglion-blocking drug is a tertiary amine—pentamethylpiperidine. Preliminary investigations suggest that its pharmacological properties resemble those of mecamylamine. It is, however, excreted more rapidly by the kidney than mecamylamine and its excretion is less affected by variation in acid-base balance. It is given by mouth as pempidine bitartrate. Tablets containing 1 mg., 5 mg. and 10 mg. are available, and the drug is usually administered at 6- or 8-hourly intervals, as its duration of effective action is shorter than that of mecamylamine: 2.5 mg. every 6 hours is a suitable initial dose, and it is then adjusted in the usual way until a satisfactory dosage level is reached. The drug is at present under trial as an oral hypotensive agent.



GANGLION-BLOCKING DRUGS IN THE TREATMENT OF  
HYPERTENSION

A detailed account of the management of patients with arterial hypertension is beyond the scope of this book, but the results of therapy with ganglion-blocking agents may be briefly mentioned.

The value of the quaternary ammonium drugs in patients with severe essential hypertension has been fully established, and many patients suffering from this condition complicated by papilloedema have lived longer than could have been expected without treatment. Symptoms such as headache are rapidly relieved, but more impressive is the objective improvement in the eye-grounds and electrocardiograms. Papilloedema, retinal hæmorrhages and exudates disappear with consequent improvement in vision, and the T-wave changes in the electrocardiogram may revert towards normal. Hypertensive heart failure may rapidly improve. Experience with the newer non-quaternary compounds is so far limited, but similar results have been obtained by oral administration of these drugs. The current trend is to employ a combination of hypotensive drugs such as rauwolfia alkaloids and a ganglion-blocking drug. A diuretic of the chlorothiazide group is often given in addition. By such combinations a satisfactory hypotensive response can often be achieved with a relatively small dose of the individual drugs, and the severity of side-effects is thereby reduced. Many different drug combinations have received clinical trial and a proper assessment of the usefulness of combined therapy must await the outcome of further clinical experience.

COMPLICATIONS OF LONG-TERM TREATMENT WITH GANGLION-BLOCKING DRUGS. The common side-effects of therapy with ganglionic blocking drugs have already been described as essential pharmacological actions of the drug. It is essential to forewarn patients so that they may recognise these untoward effects. Further, it is sometimes possible to prevent or to alleviate such side-effects, and this constitutes an important part of the management of these patients. A daily bowel action must be secured, and this can usually be achieved by the use of a

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standardised preparation of senna given at night; and if need be Magnesium Hydroxide Mixture may be given on the following morning. With severe intractable constipation neostigmine has been recommended, but its effect in patients under the influence of ganglion-blocking drugs is often disappointing. This is in accord with experimental evidence of its failure to reverse the action of blocking agents upon autonomic ganglia and it does not interfere with the hypotensive action of these drugs. Carbachol or Bethanecol are more effective and pilocarpine is also useful.

Glycerin suppositories are sometimes useful and enemata may also be required to supplement these measures. Paralytic ileus with vomiting and diarrhoea demand temporary interruption of therapy until the gut has recovered its tone. "Dryness" of the mouth may sometimes be relieved by sucking "acid-drops" and by taking beverages of citrus fruits. In more severe cases pilocarpine is the drug of choice, given every 4 hours. The dose may have to be "pushed" until an adequate effect is obtained. Pilocarpine may also be used to relieve visual disturbance due to loss of accommodation, and 1 per cent eye-drops are a useful adjuvant to oral therapy. Sometimes corrective lenses offer the most satisfactory solution to the problem. Urinary retention is best treated by carbachol or bethanecol.

Patients should be warned to assume the erect posture (for example when rising from bed) in an unhurried fashion as this simple precaution does much to prevent postural fainting. Rarely, severe hypotension may occur with loss of consciousness and the blood pressure may not be readily restored when the patient is put into the head-down position by tilting the foot of the bed. Such episodes are most likely to occur in patients with impaired renal function with consequent delayed excretion of the drug and excessively high plasma levels. Continued ingestion of a poorly absorbed preparation in the presence of severe constipation also favours their occurrence, as does the concomitant administration of systemic alkali when mecamlamine is used. Methamphetamine, mephentermine or phenylephrine should be given intravenously and a slow intravenous infusion of vasopressin has also been recommended.

A rare complication not directly due to hexamethonium has

been reported in patients treated for a prolonged period with this drug. It consisted of an organised fibrinous pulmonary œdema giving rise to dyspnœa. The changes were attributed to attacks of left heart failure modified by the hypotensive action of the drug; the patients survived for a sufficiently long time to permit organisation of the exudate to occur.

## CHAPTER 7

# DRUGS ACTING ON THE NERVOUS SYSTEM

## (other than Autonomic Nervous System)

### LOCAL ANÆSTHETICS

THESE are drugs which have a selective action in blocking the conduction of sensory nerve impulses when applied locally in suitable concentration. Loss of sensation is thus produced in the area supplied by the affected nerves. Ideally a local anæsthetic has the following characteristics: it is active both on local application and on injection, and it is non-irritant; it is not toxic on absorption and side-effects are insignificant; the anæsthetic effect is rapid in its onset and lasts long enough to allow the surgeon to complete ordinary operations. To facilitate local application and injection the drug is readily soluble in water; it is stable on boiling for sterilisation, and it does not deteriorate on storage. From the following brief account of local anæsthetics, it will be obvious that the ideal has not yet been realised.

#### COCAINE

Cocaine is an alkaloid obtained from *coca*— the dried leaves of *Erythroxylum coca*, a bush which is indigenous to Bolivia and Peru. Chemically it is methyl benzoylecgonine and it may be synthesised from ecgonine.

The essential action of cocaine is to interfere with nerve impulses in the peripheral part of the central nervous system. The precise mode of action of the drug is not known. A point of great interest and of practical importance, however, is the selective character of the action: sensory impulses are blocked before the motor fibres are affected to any appreciable extent. Further, pain sensation is the first to be affected; then appreciation of thermal, tactile and deep-pressure sensation is involved in this order.

No physical change has been detected in cocaineised nerve fibres. The effects of the drug are attributable solely to interference with physiological activity in the tissues. Anaesthesia is temporary, and sensory function is fully restored. Cocaine is a valuable surface anaesthetic because it rapidly penetrates into the superficial tissues and acts on sensory nerve endings. For practical purposes this applies only to mucous membranes and to raw surfaces; in aqueous solution cocaine hydrochloride does not produce anaesthesia when applied to the skin because of the protection afforded by the sebaceous secretion. The ability of cocaine to pass into a mucous membrane ensures its effectiveness as a local anaesthetic; it is also an important factor determining the toxic effects of the drug after absorption (see below). It follows that there is no need to inject cocaine, and indeed it is dangerous to do so. Procaine (p. 169) and other synthetic local anaesthetics are now used when it is necessary to infiltrate tissues by injection.

Cocaine constricts the arterioles at the site of absorption. The vasoconstrictor endings are sensitised to adrenaline. The blanching effect is easily visible. Its importance lies in the fact that vasoconstriction retards the absorption of the cocaine, and this is desirable because it intensifies the local anaesthetic action and also reduces the risk of systemic toxic effects.

*Cocaine Hydrochloride* (1 per cent) is commonly used in operations on the eye. Applied to the conjunctiva, it produces after momentary irritation constriction of the conjunctival vessels and the sclera is blanched. Incomplete mydriasis occurs. These actions are due to potentiation of the action of adrenaline at the sympathetic nerve endings, possibly by inhibition of amine oxidase (p. 134). The pupil of the cocaineised eye still reacts to light; and both pilocarpine (p. 119) and physostigmine (p. 115) still produce miosis. If atropine is added to the eye, further mydriasis occurs. Cocaine causes only partial loss of accommodation, and there is usually a slight reduction of intra-ocular pressure due to the vasoconstriction which follows its application: this serves to emphasise an important advantage of cocaine over homatropine (p. 128) for use as a mydriatic for diagnostic purposes in elderly patients. The anaesthetic action of cocaine on the eye lasts for about two hours,

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and as the winking reflex is abolished, the cornea tends to become dry. Dust particles alighting on the conjunctiva are not removed by the normal lachrymal flow, and this may result in local damage to the epithelium. Cocaine itself may also produce clouding and pitting of the cornea due to a direct toxic effect on the cells. For this reason cocaine should not be *repeatedly* applied to the conjunctiva.

On absorption cocaine acts as a stimulant to the central nervous system. Small doses increase the higher cerebral functions of intellect, attention and judgment; conversation is more brilliant, decisions are made rapidly and accurately, and self-confidence is increased; physical and mental energy is increased and the sense of fatigue is abolished. In susceptible persons, or with larger doses, the motor cortex is stimulated and restlessness, excitement and even delirium may appear. Stimulation of the medullary centres results in an increase in the rate of respiration, but this is succeeded by depression of the centre and breathing then becomes erratic, shallow, and may suddenly cease. The vasomotor centre may be similarly affected, and after a transient rise in the blood pressure serious hypotension develops with signs of peripheral vascular collapse. The temperature-regulating centre in the hypothalamus is stimulated and in acute cocaine poisoning, pyrexia is common. Central stimulation is soon followed by depression and death results from failure of respiration.

The heart rate is increased by cocaine probably because of increased sympathetic stimulation—both centrally and peripherally. This result is seen if cocaine is injected intravenously in error or even after subcutaneous injection in susceptible persons.

**ADDICTION.** Cocaine is a drug of addiction. Some of the effects of stimulation of the nervous system have been described above. On the higher centres this drug produces such extraordinary euphoria and exhilaration that the cocaine addict becomes completely enslaved, and ensuring that he gets regular supplies of the drug becomes the ruling passion of his life. Such is his preoccupation with self-indulgence that he becomes entirely indifferent to conventional standards of behaviour; and fear of deprivation of the drug drives him to the elaborate subterfuges

of the practised liar. Intellectual power fails; loss of self-control becomes apparent in immorality; apathy about food and cleanliness result in emaciation and unkempt appearance. At a later stage he suffers from melancholia and delusions of persecution. A characteristic hallucination is the sensation called "cocaine bugs"—in which the victim complains that insects are creeping under his skin (formication; *formis*, an ant). In addition to the mental, moral and physical deterioration, he may develop tremors of the hands and lips, nausea, anorexia and insomnia.

Addicts may take the drug by hypodermic injection: the skin of the forearms then presents a characteristic appearance on account of the innumerable puncture marks at all stages of healing and some probably showing signs of infection. Cocaine may also be taken by inhalation as snuff or what the devotees call "snow". Here the repeated vasoconstriction results in ischæmic ulceration and necrosis which often ends in perforation of the nasal septum. A moderate tolerance to cocaine is developed on continued use: doses up to 10 G. per day have been reported. In treating the cocaine addict, the drug should be withdrawn suddenly rather than gradually. Withdrawal causes severe mental depression and the patient is unable to concentrate; but the symptoms are not so severe as those of the morphine abstinence syndrome (p. 254).

Acute cocaine poisoning was not uncommon when the drug was given therapeutically by injection. It is now seen comparatively rarely, but the condition is still important because it is liable to occur as a sign of idiosyncrasy when cocaine is applied to a mucous membrane. The patient quickly becomes excited, confused, even delirious and complains of headache. There is tachycardia and breathing is shallow. Rigors may herald the onset of pyrexia; and nausea, vomiting and abdominal pain are common. The pupils are dilated. Convulsions usually precede the onset of coma and death follows from failure of respiration. Treatment consists in the intravenous injection of a short-acting barbiturate (p. 213) and the application of artificial respiration. Occasionally idiosyncrasy manifests itself in a most alarming way: painting the mucosa with cocaine solution is quickly followed by respiratory and circulatory collapse, and the patient may die in a

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few minutes. These occurrences, though comparatively rare, are so tragic that many practitioners prepare their patients by giving a short-acting barbiturate beforehand—such as a full dose of sodium amytal. Absorption of the drug from a limb can be retarded by the application of a tourniquet.

*Absorption, Fate and Excretion.* Absorption occurs from all sites of application, including the mucous membrane of the mouth, pharynx, urethra and urinary bladder. Taken orally, cocaine is rendered less effective by partial hydrolysis in the gastro-intestinal tract. After absorption, cocaine is partly detoxicated in the liver and some is excreted unchanged in the urine. The rate of destruction of cocaine is slower than that of many synthetic local anaesthetics.

*Preparations:* Cocaine Eye-drops (DDA) contain cocaine hydrochloride 2 per cent w/v and sodium chloride 0.60 per cent w/v in Solution for Eye-drops.

*Cocaine should never be used for infiltration anaesthesia.* When used in the mouth, nose or throat, cocaine may be dispensed as a 5 to 10 per cent solution or in lozenges containing from 1 to 3 mg. The practitioner should aim at using the minimal effective quantity.

A large number of synthetic local anaesthetics are available but only those in use will be discussed.

### PROCAINE ("Novocaine")

Procaine is a synthetic compound—the hydrochloride of *para*-aminobenzoyldiethylaminoethanol. A solution of procaine is stable and can be sterilised by boiling. When given by appropriate injection techniques it acts as a local anaesthetic. The skilful use of this drug has greatly increased the scope of surgical practice. Unlike cocaine, procaine is not absorbed into the superficial layers of a mucous membrane; it is therefore ineffective when it is merely painted on the mucosa. Procaine causes no irritation at the site of injection; contact with the blood vessels does not produce vasoconstriction; and after procaine has been absorbed it does not result in mydriasis. The absence of vasoconstriction is a matter



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of practical importance, for it results in rapid absorption of the drug from the tissues, and anæsthesia is therefore of short duration. The difficulty is overcome by adding a vasoconstrictor to the procaine solution: as little as 1 in 250,000 or 1 in 500,000 of adrenaline hydrochloride suffices to produce blanching by constricting the arterioles of the skin and subcutaneous tissues. A solution of procaine and adrenaline, when properly used, can result in local anæsthesia comparable to that achieved by cocaine, but without the serious hazards which attend the injection of cocaine: complete anæsthesia is established in five minutes; the effect lasts for 30-60 minutes, but even after two hours the effect may still be perceptible.

*Absorption, Fate and Excretion.* Procaine is readily absorbed following parenteral injection and is rapidly hydrolysed to *para*-aminobenzoic acid and diethylaminoethanol by the tissue enzyme, procaine-esterase, which is found in highest concentration in the liver. About 80 per cent of the *para*-aminobenzoic acid and 30 per cent of the diethylaminoethanol can be recovered from the urine; the fractions which are not excreted are metabolised.

*Toxic Effects.* Procaine has only one-quarter the toxicity of cocaine after intravenous or subcutaneous administration. Further, in clinical use, the absorption of procaine is delayed by the vasoconstrictor action of adrenaline (deliberately added to the solution of procaine); and this, in conjunction with the rapid hydrolysis of procaine, accounts for the rarity of toxic reactions. Occasionally in susceptible persons, central nervous stimulation or cardiovascular collapse may occur, as with cocaine (p. 168). The treatment is the same as for acute cocaine poisoning; and the cerebral stimulation may be prevented by giving a short-acting barbiturate orally one hour before injecting the local anæsthetic. Procaine is not a drug of addiction.

*Preparations and Routes of Administration.* Procaine is not effective on topical application. *Procaine and Adrenaline Injection* contains procaine hydrochloride 2 per cent and adrenaline hydrochloride 0.002 per cent (1 in 50,000). For infiltration anæsthesia,

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procaine is used in strengths of 0.5-1.0 per cent; for nerve block a 2 per cent solution is injected close to the nerve trunk. For spinal anaesthesia the dose of procaine is 80-200 mg. in 1.5 per cent solution. The technical details of production of the varied forms of local anaesthesia are described in textbooks on anaesthesia.

AMETHOCAINE HYDROCHLORIDE ("Anethaine") is the *para*-butylamino benzoic acid ester of dimethylaminoethanol and its solutions are stable and can be sterilised by boiling. It is about 10 times more powerful than procaine, but is proportionately more toxic; the circulatory type of toxic response is more common than the convulsive reaction.

When suitably applied to a mucous membrane it is absorbed into the superficial tissues and produces local anaesthesia in about 5 minutes; the effect lasts about one hour, but may still be perceptible after 2 hours or more. As a surface anaesthetic amethocaine can be used in 2 per cent solution. For infiltration or nerve-block anaesthesia a 1 per cent solution is adequate; spinal anaesthesia is provided by 5-20 mg. in 0.25 per cent solution.

*Amethocaine Eye-drops* contain amethocaine hydrochloride 1 per cent w/v and sodium chloride 0.69 per cent w/v in Solution for Eye-drops.

BENZOCAINE ("Anæsthesin"). Benzocaine is the *para*-amino-benzoic acid ester of ethyl alcohol. It is a surface anaesthetic and being almost insoluble in water it is used mainly as a 3 per cent dusting powder for relief of pruritus, irritation and pain. It is soluble (1 in 30) in oil and can be used in 2 per cent solution as a spray or paint on mucous membranes; the oily vehicle prolongs the contact of the benzocaine with the mucosa. *Benzocaine Compound Ointment* (benzocaine 10 per cent) is used in the treatment of anal fissure or haemorrhoids. Painful swallowing can be relieved by *Benzocaine Compound Lozenges* each containing 97 mg. of benzocaine.

ORTHOCAINE. Orthocaine is the methyl ester of 3-amino-4-hydroxy benzoic acid. It is sparingly soluble in water and is a

surface anæsthetic used as a 10-20 per cent powder diluted with starch or talc to relieve pain in wounds or ulcers. Orthocaine can also be incorporated in an ointment base in 10-20 per cent strength. It is more potent than benzocaine but, because of its tendency to cause inflammation and tissue necrosis on raw surfaces, it is little used clinically.

**BUTYL AMINO BENZOATE** ("Planoforn"). This is *n*-butyl-*p*-aminobenzoate and being almost insoluble it has a prolonged action as a surface anæsthetic. It is used as a dusting powder, in ointment, oily solution or suppositories: these preparations are similar to those of benzocaine.

**LIGNOCAINE** ("Xylocaine"). Lignocaine is *o*-diethylamino-2:6-dimethylacetanilide and is unrelated chemically to other local anæsthetics. Its solutions are stable, can be boiled and do not irritate tissues. Approximately twice as potent as procaine, it has the same systemic toxic effects as that drug, but these are very rare. It holds the advantage over procaine in that it can be applied topically as a 2 per cent solution containing adrenaline; anaesthesia develops in 2-3 minutes. Lignocaine and Adrenaline Injection contains lignocaine hydrochloride 2 per cent with adrenaline 1 in 80,000 (0.00125 per cent); infiltration with this preparation produces anaesthesia lasting up to 4 hours. Lignocaine Hydrochloride Injection is a simple solution of the drug in water and is available in strengths of 0.5, 1.0 and 2.0 per cent.

**CINCHOCAINE HYDROCHLORIDE** ("Nupercaine"). This is the hydrochloride of  $\beta$ -diethylaminoethylamide of 2-butoxycinchoninic acid. It is stable and may be boiled or autoclaved. This drug has about ten times greater toxicity than procaine and is similarly about ten times more potent as a surface anæsthetic. It does not constrict arterioles. It may cause local sloughing of tissues on subcutaneous injection and it should therefore not be used for injection anaesthesia. As a surface anæsthetic, cinchocaine can be administered in solutions of 0.1 per cent for the conjunctiva and 1-2 per cent for nose, mouth and larynx. When a solution is injected intrathecally for spinal anaesthesia, the total

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dose is 7.5-10 mg. in dilute solution (0.2-0.6 per cent). In view of its toxicity, cinchocaine should be used only by an experienced and competent anaesthetist.

*Quinine Hydrochloride* combined with urea has greater anaesthetic potency than procaine, but it causes sloughing of tissues and its use as a local anaesthetic is obsolete.

## CENTRAL NERVOUS SYSTEM STIMULANTS

**INTRODUCTION.** These are drugs which increase the activity of various parts of the central nervous system. The stimulating effect is not evenly distributed, and indeed the uneven pattern of activity in the nervous system and elsewhere is often characteristic of the individual substance or the group to which it belongs chemically. The therapeutic value of stimulants is to some extent limited by this multiplicity of actions. The effect of strychnine provides an extreme example: serious overdose or cumulation may result in muscle twitchings passing on to tetanic convulsions. Again, the sympathomimetic amines may cause restlessness, cardiac arrhythmias and dysuria. Many side-effects of the kind mentioned can be avoided by adjusting the dose of the drug; but if they are unavoidable and intolerable the drug will not be retained for therapeutic use. In general, therefore, selectiveness of pharmacological action is highly desirable—as in the case of stimulants of the vital centres of the medulla. It should not be assumed, however, that side-effects invariably constitute a disadvantage, for the distinction between “main effect” and “side-effect” is arbitrary. A group of drugs chemically related to one another may share in varying degree a stimulating action on the vital centres. The side-effects of these drugs may differ considerably, but this variation may actually enhance their potential therapeutic value. The physician is able to select from the group of drugs one which is well suited to the individual patient's needs. In such circumstances a “side-effect” of a drug may be of greater value than its main pharmacological action.

These general principles apply to the series of drugs mentioned below. Their individual pharmacological characteristics are ex-

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ploited therapeutically according to the physician's assessment of the patient's requirements: the pharmacological stimulus may be needed at any "level" —from the cerebral cortex to bulbar or spinal reflex arc.

### PICROTOXIN

Picrotoxin is obtained from the seed of a climbing shrub, *Anamirta cocculus*. It is dispensed for intravenous or intramuscular injection in aqueous solution containing 3 mg. in 1 ml. It is a powerful central nervous system stimulant, the most prominent effects being on the respiratory and vasomotor centres in the medulla. In the treatment of the central depression due to overdosage with barbiturate or other sedative drug, picrotoxin causes respiratory stimulation and raises the blood pressure.

Following on intravenous injection in experimental animals, only traces of the drug can be found in the blood after 20 minutes. Its distribution and fate within the body are unknown.

Toxic doses stimulate the cerebral cortex and the spinal cord, giving rise to localised muscle twitching, firstly of the face, followed by generalised convulsions. These have been termed "coordinated", in contrast to the convulsions produced by strychnine in that the limbs are alternately flexed and extended. This stimulation is rapidly followed by extreme central depression and death may then ensue from respiratory failure. The therapeutic dose of picrotoxin is close to the toxic dose and the drug should only be given in small doses of up to 3 mg. at intervals of 15-30 minutes. In the treatment of poisoning by sedatives, it has been largely replaced by bemegride (see p. 691) or amphetamine (see p. 690).

### CAFFEINE

Caffeine, which is present in tea and coffee, acts chiefly as a stimulant to the central nervous system. Caffeine is trimethylxanthine and has many pharmacological actions like the other xanthines, theophylline and theobromine. The diuretic effect of xanthines is described on p. 41.

Caffeine, being bitter, acts as a sialogogue. Moderate doses

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produce an increased secretion of gastric juice; thus a caffeine test meal can be used in studies on gastric secretion.

Caffeine excites all parts of the central nervous system. The sensory cortex is first affected producing an increase in sensory perception. There is a clearer flow of thought, a more rapid association of ideas, and postponement of muscular fatigue and drowsiness. The motor area of the cortex is also stimulated giving increased speed of movements. Recently acquired motor skill, especially if associated with delicate coordinated movements may be adversely affected. Conditioned reflexes are augmented. These effects of caffeine are found after a therapeutic adult dose of about 250 mg., the amount contained in one or two cups of rather strong tea or coffee.

The medullary centres are stimulated by larger doses, and caffeine can be used for this purpose in patients suffering from sedative poisoning. The respiratory, vasomotor and vagal centres are affected. If breathing is depressed in sedative poisoning, both the rate and depth are increased by caffeine; the mode of action possibly includes a process of sensitisation of the respiratory centre to carbon dioxide. The cardiac rate may be slowed by central vagal stimulation, but the effect on the arterial blood pressure is unpredictable owing to the combined central and peripheral effects of caffeine on the cardiovascular system. Massive doses given to animals cause excitability of the whole central nervous system, including the spinal cord. Reflex excitability is increased, clonic convulsions occur and death may ensue.

Of all the xanthines caffeine has the least effect on the cardiovascular system. In man, the predominant actions of caffeine on the central nervous system preclude its use for its cardiovascular effects. Caffeine stimulates the myocardium, directly increasing the cardiac output. In perfusion experiments caffeine increases the cardiac rate, but in the intact animal the central vagal stimulation tends to slow the heart rate. In man after therapeutic doses, bradycardia or tachycardia may occur. After large doses of caffeine, tachycardia and sometimes cardiac irregularities (premature beats) occur due to stimulation of the myocardium. There is simultaneously a fall in the venous filling pressure of the heart. On the blood vessels, caffeine has also a dual effect. Stimulation

of the vasomotor centre causes constriction of peripheral blood vessels, but the direct action of the drug on the vascular musculature produces vasodilatation. After therapeutic doses the dilator effect predominates. The increased cardiac output and the arteriolar dilatation result in an increased peripheral blood flow. Cerebral blood flow is diminished by caffeine owing to an increase in cerebrovascular resistance. The use of caffeine in analgesic mixtures for the treatment of headache is based on this fact. Caffeine dilates the coronary arteries. The effect on arterial blood pressure varies, being the resultant of the combined actions of caffeine on the myocardium and on the peripheral vessels; it usually consists of a rise in systolic pressure of not more than 10 mm. of mercury. Caffeine is rapidly absorbed after oral or parenteral administration. It is partially demethylated and oxidised, being largely converted to methyluric acid in which form it appears in the urine. It can be detected in the blood for 6-12 hours after administration.

Toxic doses produce insomnia and restlessness which may proceed to delirium, disturbances of the special senses with tinnitus or flashes of light. Tachycardia and extrasystoles are common. If a fatal dose is given to animals caffeine causes convulsions followed by respiratory failure.

For oral administration, either the free Caffeine base or a soluble double salt may be used, e.g. Caffeine Citrate or Caffeine and Sodium Benzoate. A suitable preparation for intramuscular injection is Caffeine and Sodium Benzoate in a dose of 500 mg.

**STRYCHNINE.** Strychnine is obtained from the seeds of a tree native to India, *Strychnos nux-vomica* (so called from the shape of the seeds). Both strychnine and nux vomica have a very bitter taste, and in very small doses their preparations have been used as bitters (p. 398). Therapeutically, however, strychnine is obsolete: its pharmacological actions are described here because they are of scientific importance.

Strychnine is rapidly absorbed from the intestine and exerts its main action on the spinal cord. In low dosage it increases the reflex excitability of the spinal cord, with the result that skeletal muscles react in an exaggerated but coordinated manner. The

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threshold for sensory stimuli is lowered, the subject becomes more responsive to external stimuli and the tone of the voluntary muscle is therefore increased. If a toxic dose is administered, coordinated activity in the spinal cord is lost. A minimal sensory stimulus spreads along the spinal cord instead of following the localised physiological reflex arc, and in consequence, numerous widely separated voluntary muscles contract simultaneously. This causes a "spinal convulsion" in which both the flexor and extensor muscles participate simultaneously, but as the extensors are usually more powerful a characteristic posture results. In man the legs are rigidly extended and the trunk is arched (opisthotonus) so that only the crown of the head and the patient's heels may be touching the ground. The legs are adducted and the feet inverted. The arms may be rigidly flexed on the thorax, or held extended, the fists clenched. The angles of the mouth are drawn back in an unnatural grin (risus sardonicus) and the jaws are tightly clenched (trismus). Spasm of the respiratory muscles causes respiratory arrest during the convulsion with temporary signs of asphyxia. As strychnine also stimulates the cerebral sensory cortex, the patient is hypersensitive to all sensations accompanying the painful muscular contractions. The convulsion may last as long as 60 seconds: the muscles then relax in a state of fatigue and respiration is resumed. Within a few minutes reflex excitability rapidly increases and another convulsion ensues. Death is caused by asphyxia due to medullary paralysis.

The stimulation of the sensory cortex by strychnine makes the senses of taste, touch, hearing and smell more acute. Visual acuity also improves but this may be due to a local effect of the drug on the retinal cells rather than to a central action. The respiratory centre in the medulla is stimulated by strychnine, but only after a dose greater than that which produces increased excitability of the spinal cord. It is only in cases of sedative poisoning where there is depression of both spinal cord and medulla that this respiratory stimulating action of strychnine can be utilised.

On the heart and blood vessels, strychnine has no direct action in subconvulsive doses and there is no rational basis for its use as a cardiac stimulant. In therapeutic doses, the effect on blood



pressure is unpredictable. The marked rise in blood pressure during a spinal convulsion is merely a consequence of muscular exertion.

Voluntary muscles are not affected by therapeutic doses of strychnine. Similarly, smooth muscle is not stimulated by the drug. The use of strychnine in the treatment of gastro-intestinal muscle atony— or to enhance the activity of purgatives—is based on inadequate evidence.

Strychnine is readily absorbed after oral or parenteral administration. It rapidly leaves the blood stream and is mainly destroyed in the liver; about 20 per cent of the alkaloid is found in the urine. Excretion is almost complete after 10 hours but traces of the drug may be found for several days. Preparations of strychnine are commonly prescribed for their reputed “tonic” effect. It is now believed, however, that the only rational therapeutic use of strychnine is to alleviate respiratory depression in sedative poisoning. Even then, *it is not the stimulant drug of choice because of its dangerous side-effects.*

Brucine, another alkaloid obtained from *nux vomica*, acts like strychnine but is very much weaker.

### NIKETHAMIDE

Nikethamide is a synthetic, water-soluble derivative of nicotinic acid. It acts on the chemoreceptors in the carotid body, reflexly stimulating the respiratory centre in the medulla. In patients with the respiratory depression of sedative poisoning, nikethamide given intravenously causes an increase in the depth and rate of respiration. The dose of the official Injection of Nikethamide is 1–4 ml., but as much as 20 ml. may be needed if there is considerable depression of the respiratory centre. A rise in blood pressure may occur from vasoconstriction but the effect is not marked. It is not a direct cardiac stimulant and has no effect on the coronary circulation in therapeutic doses. Large doses of nikethamide cause tremors and convulsions. The stimulating effects of nikethamide are not seen after oral administration and it is therefore useless to give this drug by mouth. Nikethamide Injection contains 25 per cent w/v of Nikethamide.

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### LEPTAZOL

Leptazol is the synthetic compound 1:5-pentamethylenetetrazole. It has the property of stimulating the central nervous system. Its actions are similar to those of picrotoxin but it is a less toxic drug. It is given parenterally (100 mg. in 10 per cent solution) to patients in sedative poisoning, because it stimulates directly the depressed medullary respiratory and vasomotor centres. Leptazol has no significant direct action on the myocardium or blood vessels. In full doses intravenously leptazol causes convulsions by its action on the motor cortex and this effect was formerly applied by psychiatrists using convulsion therapy, but electrical stimulation is now preferred.

### AMPHETAMINE

Amphetamine ("Benzedrine") is a synthetic sympathomimetic drug (see p. 141) which has a powerful cerebral stimulant effect. The mode of action on the cells of the central nervous system is unknown. Administered intravenously or intramuscularly in a dose of 50 mg. to patients in coma due to an overdose of a sedative drug, it shortens the recovery phase. This effect may be due solely to its action on the cortex, but may also be partly due to activation of the arousal mechanisms of the brain-stem. The dextro-rotatory form, Dexamphetamine, is twice as potent a cerebral stimulant as amphetamine, a suitable parenteral dose being 30 mg.

### BEMEGRIDE

Bemegride ( $\beta$ -methyl- $\beta$ -ethyl glutarimide) is a synthetic preparation. It acts as a stimulant to the central nervous system; and it is used therapeutically to accelerate the recovery of patients suffering from overdosage with sedatives. Originally it was thought to have a specific effect which was antagonistic to the barbiturates, but it is now considered to be a non-specific central stimulant. The site of action is unknown: it may be in the reticulocortical activating system, which links the cerebral cortex and the reticular nuclei in the brain-stem. Bemegride is administered intravenously in a dose of 50 mg. in 10 ml. of saline; this

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dose can be repeated at intervals of 5 minutes until it is apparent that there is lessening of the depth of coma. The first obvious effect of bemegride is to increase the depth and the rate of respiration. This is followed by return of the corneal, cough and swallowing reflexes. Full recovery of consciousness may not occur under stimulation with bemegride without the appearance of side-effects. Injection of excessive amounts may lead to retching or vomiting, twitching of muscles, especially of the face and hands, and even generalised convulsions. Formerly, picrotoxin was used as the specific antidote in barbiturate poisoning and there are many reports of satisfactory results from this treatment. However, with only slight overdose of picrotoxin there is a greater risk of causing convulsions, and the drug has been abandoned in favour of bemegride which has greater latitude of therapeutic action.

### AMIPHENAZOLE

Amiphenazole (2:4-diamino-5-phenylthiazole hydrochloride) is a synthetic drug with a stimulant effect on the respiratory centre in the medulla. It is therefore used in cases of poisoning caused by sedatives. The dose is 15 mg. by the intravenous route, and this can be repeated at intervals of 5 minutes. It has been widely used in conjunction with bemegride in the treatment of overdosage with sedative drugs. In patients suffering from respiratory depression due to *morphine* and related drugs, the action of amiphenazole is inferior to that of nalorphine. (see p. 258).

## CENTRAL NERVOUS SYSTEM DEPRESSANTS

### Alcohol

The most important action of ethyl alcohol is upon the central nervous system. Here its depressant properties are closely akin to those of the methane series of anæsthetics such as chloroform and ether and the hypnotics of the chloral hydrate group.

Alcohol is valued as a beverage because it promotes a feeling of well-being and contentment which may be difficult to attain by any other means. The changes of temperament which occur after even small quantities of alcohol are well known. A man who is normally of a retiring disposition becomes communicative and

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self-assertive. At the same time the drinker is pleasantly aware of a sense of mental and physical relaxation. Pressing problems or anxieties become much less poignant and cease to dominate his outlook on life. Instead of pre-occupation there are clear indications of a desire to avail himself fully of the pleasures of the moment.

After large amounts behaviour often becomes boisterous. Speech is loud, and tedious repetition with over-emphasis are characteristic. The main subject of conversation is usually the remarkable attributes of the speaker. Phraseology is needlessly extravagant. Judgment is fallacious. Symptoms of this kind also predominate in the public speeches of those who are the worse for alcohol: the speaker radiates inordinate satisfaction over an effusion which may be little removed from nonsense. Even at this stage there may be some difficulty in maintaining an upright position and delicate movements calling for fine coordination are often impaired. In some circumstances there are further manifestations of loss of self-control and conduct may become indecorous to the point of indecency.

Acute alcoholic intoxication results in a condition of drowsiness and physical helplessness. Unsteadiness and lurching produce the typical drunken gait. In severe cases the drunkard sooner or later falls to the ground unless he can find support. Diction is noticeably altered and the speech is said to be "thick". Absurd attempts are made to pronounce polysyllabic words and in hesitating over such difficulties the speaker often forgets the endings of his sentences. In this stage of poisoning the face is pale and even haggard. Nausea and vomiting add to his discomfort and humiliation, but finally he is overwhelmed by the desire to sleep. In alcoholic *coma* there is complete loss of the sensations of pain and touch. Muscles relax, reflexes disappear and some resemblance to chloroform and ether anaesthesia is seen in the slow stertorous breathing and cyanosis.

*Action of Alcohol.* From the beginning to the end of its action alcohol depresses the nervous system. The view almost universally held by the lay public, that in moderate quantities alcohol is a stimulant, is based on a misinterpretation of the symptoms and

signs. Alterations in behaviour accompanied by increased self-confidence, loquacity, etc., must be regarded as "release phenomena" due to depression of the most recently acquired critical faculties which normally promote self-restraint.\* By careful observation it is possible to follow the march of paralysis from the highly susceptible intellectual centres to the more resistant vital centres in the medulla. Even the intermediate stages of physical animation and depressed sensitivity can be identified almost as clearly as in the case of the general anæsthetics ether and chloroform.

Many tests have been devised to estimate efficiency in various kinds of physical and mental work after taking alcohol. The ability to do simple arithmetic or to memorise a row of figures is obviously impaired. Reaction time may be diminished so that a quicker response is obtained; but when the drinker is presented with a choice of actions alcohol is seen to interfere with accuracy of response, and mistakes are more frequent. Games of skill such as billiards—in which manual dexterity and judgment are required—quickly reveal the ill-effects of alcohol upon efficiency. Notwithstanding objective proof to the contrary, it is characteristic that the person concerned is always convinced that his performance has been greatly improved by indulgence in alcohol.

The animated condition which develops soon after taking alcohol accounts for a sudden increase in the amount of work done but within an hour efficiency falls to a low level and recovery may not occur for several hours. Throughout this time, however, the sense of fatigue is markedly diminished, and it is this which gives rise to the false impression of greater efficiency. In other words, for prolonged muscular exertion alcohol seriously impairs efficiency, but when a short burst of physical activity is contemplated the work done is sometimes increased.

*Absorption and Excretion.* Alcohol is rapidly absorbed from the stomach and upper intestine and circulates in the blood stream. Except for about 2 per cent which is excreted in the urine it is broken down to carbon dioxide and water. Oxidation in the tissues is slow (about 10 ml. per hour) and hence repeated dosage at short intervals is likely to cause cumulation and intoxication. On com-

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bustion, 1 G. of alcohol yields 7 calories and it can be used to supplement the carbohydrate and fat of the food, thus tending to spare the body proteins. However, the *habitual* use of alcohol for this purpose is unjustifiable because the ability to metabolise alcohol to advantage is acquired only slowly over a period of several days and its depressant action upon the nervous system may seriously prejudice the general care of the patient. The use of dilute alcoholic beverages (beer and stout) over a period of years often leads to obesity because weak alcohol supplements the ordinary food without causing gastric irritation or seriously delaying digestion. Strong alcohol, however, taken "neat" -- though of high calorific value—is apt to produce gastritis and impair the appetite for regular meals. Not infrequently, therefore, spirit-drinkers are poorly nourished. The absorption of alcohol is retarded, if a copious draught of milk is taken first; but it is accelerated by taking water.

*Alimentary System.* In the mouth alcohol stimulates the gustatory nerves and produces reflexly an increase in the flow of saliva and gastric juice, thus stimulating the appetite and favouring digestion. The psychic value of the bouquet of wines and liqueurs undoubtedly plays a very important part in this action. Mild irritation of the gastric mucosa may contribute to the same effect. On the other hand, when the amount of alcohol in the stomach exceeds 3 per cent enzyme action is delayed and digestion is retarded. In small quantities the stronger alcoholic preparations such as brandy are highly valued as carminatives in the stomach and bowel: the tonus of involuntary muscle is depressed and the relaxed sphincters allow gas to be expelled.

*The Heart and Blood Pressure.* It has been proved by laboratory experiment that alcohol in dilute solution (0.4 per cent) can be utilised as a food by the isolated heart and the strength of systole is thus increased. When the concentration is gradually raised the force of the heart beat improves but 0.8 per cent of alcohol proves poisonous to the heart muscle and contractions become weaker until they cease altogether. Properly controlled investigations in man show that alcohol has no effect upon the rate of the

normal heart. Aromatic substances commonly found in alcoholic beverages may reflexly increase the heart rate, especially in fainting conditions. Changes in the blood pressure attributable to alcohol alone are insignificant: constriction of the splanchnic vessels causes a slight elevation of blood pressure but cutaneous vasodilatation tends to produce the opposite effect. The action of alcohol upon the superficial vessels is of some practical importance as it accounts for the sense of warmth, increased sweating and a fall of temperature often amounting to about  $1^{\circ}\text{C}$ .

*Respiration.* Moderate doses of alcohol such as might be used in therapeutics have no important action on the respiratory centre. Any changes that have been observed are inconstant and variable. The irregularities of respiration seen in alcoholic intoxication are mainly the result of associated conditions such as physical and mental animation, drowsiness or actual narcosis. Ethereal substances in many alcoholic beverages may stimulate respiration reflexly so that the rate is noticeably increased.

*Urinary Output.* Alcohol is credited with slight diuretic properties. The action has been attributed to the direct action on the kidney or to an improvement in renal blood supply. There is experimental evidence, however, that pure alcohol inhibits posterior pituitary secretion. This observation—which suggests that the pharmacological action of alcohol is identical with the physiological effect of water—is a matter of considerable academic interest. In clinical practice, however, the diuretic effect of alcohol is unimportant: when taken in the form of dilute beverages the diuretic effect is mainly attributable to the increased intake of water: there is little or nothing to be said in favour of ordering alcohol or alcoholic beverages to promote diuresis.

*Externally,* alcohol is an antiseptic. Its optimum strength for this purpose is 70 per cent *by weight*, and minor variations seriously affect its potency. It acts by dehydrating the superficial tissues and precipitating proteins. This astringent effect is utilised in hardening the skin of the nipples to prevent cracking and sepsis during suckling; and in preparation for long walks or route marches, the frequent application of absolute alcohol to the feet

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makes the skin less liable to blister. In weaker solutions (30 per cent) alcohol is used to lower the temperature of the body by sponging the skin and allowing free evaporation. A rubefacient and counter-irritant effect can be produced by applying strong alcohol to the skin and covering the part to prevent evaporation. When alcohol is injected into a nerve it causes local destruction of the tissues and this action was formerly applied in the treatment of some forms of intractable pain. Thus in cases of intractable trigeminal neuralgia absolute alcohol was sometimes injected into the Gasserian ganglion, but the method has been abandoned in favour of surgical operation for section of the appropriate division of the trigeminal nerve.

**CHRONIC ALCOHOLISM.** The harmful effects of continued abuse of alcohol are well known. At the same time individual susceptibility varies greatly, and this accounts for the fact that alcoholism is by no means incompatible with longevity. Further, the habitual drinker rapidly acquires a tolerance which enables him to ingest toxic doses without immediate untoward effects. This is accounted for by an increased facility in oxidising the drug and a more rapid rate of excretion. Among the most striking effects of chronic alcoholism is deterioration of the highest mental faculties governing personal and social behaviour. Physical grossness gives place to emaciation if alcoholic beverages are strong enough to cause gastric disturbances and indifference to food. Other symptoms and signs are attributable indirectly to malnutrition, diminished exercise tolerance and liability to infections of the respiratory tract.

Many highly characteristic clinical syndromes are associated with alcoholism, e.g. peripheral neuritis, Korsakow's psychosis, alcoholic pseudoparesis, delirium tremens and dipsomania. These conditions and their management are dealt with in textbooks of clinical medicine and psychiatry. Cirrhosis of the liver is not infrequently associated with chronic alcoholism. The fibrosis is apparently not a reaction to the *direct* effects of alcohol on the liver, but the sequel to degeneration of liver parenchyma which is the consequence of malnutrition—so commonly seen in the chronic alcoholic.



**THERAPEUTIC USES.** Although alcohol in the form of intoxicating beverages is used widely by the lay public as a panacea, it is difficult to find any justification for the practice by strictly scientific standards. This is not to say that alcohol lacks beneficial effects. It is a valuable sedative and carminative. These actions can be achieved by means of other drugs available to the physician, but in practice patients usually prefer alcoholic beverages which produce the desired effect and simultaneously promote a feeling of well-being. Alcoholic beverages, usually in the form of hot toddy, are commonly used by the lay public to abort colds and chills. The effect is to lower the temperature and produce sweating by vasodilatation, while the action of alcohol in abolishing anxiety and promoting sleep contribute to its popularity. Alcohol, preferably as whisky, is often a valuable hypnotic for the nervous insomnia of old people. Its use for this purpose in young or middle-aged individuals is rarely justifiable and in all circumstances the possibility of habit-formation must not be overlooked.

The external uses of alcohol have been mentioned. Vast quantities of alcohol are, of course, used in the manufacture of pharmaceutical preparations and in the chemical industry.

Formerly alcohol was employed in the "routine" treatment of many acute infections, notably in pneumonia and various infectious diseases. While it cannot be denied that by judicious dosage alcohol can act as a valuable food substance in these and other conditions, it is no longer believed that it has any peculiar beneficial action on the course of the illness. In some hospitals the medicinal use of alcohol has been abandoned altogether without any apparent disadvantage.

The weaker alcoholic beverages such as beers and wines are sometimes prescribed effectively in loss of appetite and chronic malnutrition, especially in convalescence after debilitating diseases. Most of the improvement that occurs in these circumstances is due to the stimulating action of the higher esters which account for the "bouquet" of wines. In addition the factors of suggestion and a sense of relaxation operate to a considerable degree. The calorific value of a small quantity of wine is negligible. Loss of appetite in neurasthenic subjects should not be treated by the use of alcohol owing to the greater liability to habit formation.

## GENERAL ANÆSTHETICS

INTRODUCTION. When major surgical operations are to be carried out, it is nearly always desirable that the patient should be unconscious and also unable to appreciate pain (anæsthesia). These fundamental considerations have been recognised for a long time (*Genesis*, ii. 21). It has also been known from time immemorial that when a man has been rendered unconscious by excessive doses of certain narcotic drugs, he can sustain severe physical trauma (lacerations, dislocations, fractures, etc.) and have no recollection of feeling pain at the time of the injury. This may occur, for example, when a man is "dead drunk" from the effects of alcohol (p. 181). The use of alcohol as a general anæsthetic, however, would be now regarded as a crude form of medical practice: such large quantities of alcohol are required that the patient is in imminent danger of dying from the depressant action of the drug on the vital centres in the medulla. And those patients who survive the experience emerge in a state of subacute toxæmia complicated by dehydration, gastritis and hepatic dysfunction: these conditions together account for prostration, intense headache and vomiting. The possibility of experiencing after-effects of this severity would deter any thoughtful patient from submitting to induction of general anæsthesia through the medium of alcohol. There are other drugs which, in large doses, produce coma and anæsthesia. They include Indian Hemp, used in this way by Chinese surgeons in the 2nd century A.D., and Opium, which was administered as a general anæsthetic by practitioners of the Salerno School of medicine in the 12th century. Here again, however, the toxic effects of these narcotics when given in appropriate doses made the procedure hazardous: the chief danger was death from respiratory failure following depression of the vital centres. It is clearly necessary to turn to other drugs which have a *selective action* on the higher centres of the brain and on the sensorium, and which do not cause serious toxic effects elsewhere in the body. It is a curious fact that such drugs do exist and they are all products of man's ingenuity as a synthetic chemist and experimentalist. Even more remarkable is the historical fact that the pharmacological actions

of the substances properly described as general anæsthetics were discovered more by accident than design.

The intoxicating effect of *nitrous oxide* was recorded by Sir Humphry Davy in 1799, and he added that it might be "used with advantage in surgical operations". In 1815 Michael Faraday noted that ether had similar effects. Another experimentalist in this field was a Shropshire practitioner, Dr. Henry Hickman: he showed that when animals inhaled a mixture of nitrous oxide and carbon dioxide they became unconscious and insensible to pain. He suggested that the method should be applied in the practice of surgery. In their own country scant attention was paid to these pioneers, and the development of general anæsthesia in relation to the practice of dentistry and general surgery became part of the history of medicine in North America. The date of Michael Faraday's original observations on ether (1815) is noteworthy. In that year Crawford Long was born and he became a country doctor in Jefferson, Georgia, U.S.A. As a young man of 27 Dr. Long fulfilled Faraday's forecast: he used ether to anæsthetise a boy, and excised a tumour from the patient's neck. Ether as a general anæsthetic gradually became established in various parts of the world. In obstetric practice, however, its limitations as an anæsthetic prompted James Young Simpson of Edinburgh to look for a more powerful drug. It was James Waldie, a Liverpool chemist, who suggested to Simpson that chloroform might be effective. The circumstances in which chloroform was tested provide one of the dramatic episodes in medical history.\* In the 20th century new anæsthetics have been synthesised and ingenious apparatus invented to facilitate administration. The induction and maintenance of general anæsthesia are never entirely free from hazards—though under ideal conditions the risk of toxic effects almost vanishes. Among the factors which determine the nature of the risk are the toxicity of the drug itself, the susceptibility of the individual patient to the toxic action of the anæsthetic selected, the presence or absence of disease (including obesity), the proficiency of the anæsthetist and those who assist him, the nature of the operation and its duration, the skill and judgment

\* Douglas Guthrie's *History of Medicine* includes an interesting account on this subject, and also a valuable bibliography.

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of the surgeon, and so on. Thus a drug which is potentially toxic is often used successfully as a general anæsthetic, and the opposite result may be seen from a "safe" anæsthetic. These apparent anomalies are nearly always explained in terms of the skill and judgment of those who attend the patient.

Broadly, the anæsthetist's objectives are to give enough of the drug to induce (a) loss of consciousness, (b) the state of insusceptibility to painful stimuli, and (c) a degree of muscular relaxation which permits the surgeon to work without hindrance. If the anæsthetist depends exclusively on the general anæsthetic in order to achieve these effects, he will often need to give large quantities of the drug and thus expose the patient to a greater risk of poisoning or to other complications. There are two phases in particular when such hazards are conspicuous. (1) If the stage of induction of anæsthesia is not to be unduly protracted an appropriate concentration of the anæsthetic in the blood stream must be attained in the course of the first few minutes of administration. However, the speed of induction can be considerably increased and the demand for a volatile anæsthetic (such as ether) diminished by the procedure known as *premedication*. This consists in creating a state of basal narcosis so that the patient is already drowsy (perhaps even unconscious) as a result of preliminary administration of barbiturates (usually thiopentone), and therefore well on the way to the state of anæsthesia before the volatile anæsthetic is given. Again, going back to an earlier stage in the management of the patient, he usually receives morphine and hyoscine about an hour before the time of operation. The primary objectives in giving these drugs are to diminish secretion in the mouth and the upper respiratory tract and render the heart less sensitive to vagal inhibition. Both of them, however, have a sedative effect and hence their actions on the higher centres can be regarded as the initial phase of induction of basal narcosis—which is completed later by means of thiopentone. (2) Another "peak demand" for a general anæsthetic often occurs in the course of abdominal operations. For example during the removal of a diseased and shrunken gall-bladder the surgeon insists on a degree of anæsthesia which ensures full relaxation of the abdominal muscles in order to give him access to the field of operation. Here

again premedication plays a part in enabling the anæsthetist to create suitable conditions with relatively small quantities of volatile anæsthetic. The modern practice, however, is to depend not on deep anæsthesia but on *muscular relaxants* of the *d*-tubocurarine type; these are given after the patient has been anæsthetised and at an appropriate moment in anticipation of the requirements of the surgeon.

Anæsthetic practice now closely approximates to applied physiology and applied pharmacology. Precision in methods of administration has been achieved by means of more or less elaborate apparatus which has become standard equipment in operating theatres. The greater choice of anæsthetics and ancillary drugs, and insistence on skill in handling them are some of the factors that have contributed to the development of surgical techniques in hospitals. In countries which have a Health Service developing on appropriate lines, there is a diminishing need to resort to the old and relatively crude forms of "open" anæsthesia—chloroform or ether allowed to drip on a gauze mask held over the patient's mouth and nose; those who require surgical operation are transported rapidly to hospital so that they may have the advantages of specialist management. If, however, the needs of patients throughout the world are considered, it is obvious that only a small minority receive the ideal kind of medical and nursing care; and relatively few are dealt with by specialist-anæsthetists. It follows that the great majority of doctors need to be acquainted with the open method of inducing anæsthesia, for the techniques of medical practice are determined largely by the exigencies of the day and by local circumstances. As a further illustration a brief reference may be made to the relative merits of ether and chloroform. In this country today few doctors could justify continuing to use chloroform, for other things being equal—ether is to be preferred on account of its low toxicity. Nevertheless, in hot climates it may be entirely impracticable to use ether by the open method because of its high volatility: chloroform, on the other hand, might be used without difficulty. Again, the single-handed doctor working under adverse conditions in a tropical station would find chloroform much more convenient, being more potent (small bulk) and non-inflammable.

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In the following account of general anæsthetics little is included about methods of administration: the techniques of the specialist-anæsthetist are beyond the scope of this book; and the open method of administration (ether, chloroform, ethylchloride) (mentioned below) is learnt only by practical instruction from an experienced teacher in hospital.

### CHLOROFORM

Chloroform, if inhaled in the form of vapour freely mixed with air, reaches the tissues very rapidly. It requires 2 per cent of chloroform vapour in air to induce anæsthesia and about 1 per cent to maintain it, while 3-4 per cent in air will soon produce respiratory failure. A concentration of 0.02 per cent in the blood and tissues is necessary for light anæsthesia; from 0.025 to 0.035 per cent maintains surgical anæsthesia; whilst 0.04-0.07 per cent can cause respiratory failure; the margin of safety is, therefore, small. The following description of the phenomena of anæsthesia has special reference to chloroform, but it is also applicable to other general anæsthetics, particularly diethyl ether, if the differences in action be noted.

I. PHENOMENA OF CHLOROFORM ANÆSTHESIA. (a) *First stage of irritation and blunted perception or analgesia.* The inhalation of chloroform irritates the nasal, laryngeal, and buccal mucous membranes, and may cause sneezing, coughing and salivation; the irritation of the fifth nerve in the nose often causes, reflexly through the medulla, temporary cessation of respiration and momentary retardation of the heart. Perception and the imagination are exalted but confused; there is a sensation of roaring in the ears; and vision, hearing and touch are more or less disturbed. The pulse becomes more rapid, blood pressure rises, respiration is slightly accelerated, the pupils dilate, and the face is flushed.

(b) *The second stage* is characterised by depression of the higher cerebral centres and unrestrained activity of the motor centres, which are now deprived of the higher inhibitory control. Various

incoordinate gesticulations, spasms, and reflex or protective struggling movements ensue; and the patient often becomes talkative although the speech is thick and ideas are confused. Respiration is irregular owing to the struggling; the pulse is accelerated; blood pressure is raised, especially during periods of struggling; the pupils are dilated, the eyes move from side to side, and the skin is flushed or cyanosed. During this stage the patient is unconscious and does not actually feel pain, but the reflexes, both spinal and medullary (vasomotor and respiratory), are still present.

(c) *Third stage.* With the onset of the stage of surgical anaesthesia, the muscular movements gradually diminish, the muscles relax and reflex action is abolished, the corneal reflex being one of the last to disappear. The pulse is slower and weaker; blood pressure falls below normal; respiration is regular but slow and shallow, and often snoring owing to closure of the fauces by the relaxed tongue. The pupil becomes contracted as in sleep and fails to react to light, and the temperature of the body tends to fall (depression of the thermogenetic centre, and the state of muscular quiescence). Anaesthetists divide the stage of surgical anaesthesia into four planes of increasing depth. When the stage of surgical anaesthesia has been established, it is safe to operate. Prior to this, surgical interference with sensitive parts will excite reflex movements and may lead to reflex inhibition of the heart and respiration, or to ventricular fibrillation.

(d) *The fourth or danger stage.* This is characterised by the onset of paralysis of the medullary centres. Depression of the respiratory centre results in weak, irregular, sighing, or periodic respiration which may fail suddenly. The onset of asphyxia is indicated by sudden wide dilatation of the pupils and by cyanosis of the lips, ears and finger-nails. As the heart muscle is now seriously poisoned, the pulse becomes feeble and irregular. The vasomotor centre is depressed, and dilatation of the splanchnic vessels adds to the effect of cardiac failure in lowering the blood pressure; the skin appears pale and wax-like. In this stage the anal and bladder reflexes are abolished. Death may occur either from respiratory or cardiac failure.

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2. ANALYSIS OF THE PHENOMENA OF CHLOROFORM ANÆSTHESIA. (a) *Nervous system.* The action of chloroform on the nervous system closely resembles that of alcohol. It rapidly depresses the higher psychic, inhibitory and perceptive centres, and the uncontrolled speech centre and motor area may initiate garrulous incoherent talk, gesticulation and resistant struggling. As the sensory area becomes depressed, pain is abolished, and soon (from paralysis of the motor cortex) the patient becomes quiescent; it has been shown that at this stage the motor area is less sensitive to electrical stimuli. Abolition of the spinal-cord reflexes follows: the first to disappear are those of the back and limbs, then those of the abdomen and genital organs, next the corneal and light reflexes and, later, the sphincter reflexes of the bladder and rectum. Depression of the medullary reflexes occurs last. The sensory neurons are paralysed before the motor neurons. This can be demonstrated experimentally. By preliminary removal of the pia mater, a segment of the cord may be made inaccessible to chloroform in circulation. At the stage when the anæsthetic has abolished spinal reflexes in other parts of the cord, stimulation of the intact sensory nerves at the selected segment produces reflex contraction of muscles which receive their motor-nerve supply from other segments.

*Theories of Narcotic Action.* Many suggestions have been made to account for the action of the general anæsthetics and organic hypnotics. The Meyer-Overton theory takes as its basis the fact that all aliphatic compounds producing narcosis are easily soluble in fats and lipoids, and suggests that in the brain these compounds form with the lipoids of the nervous cells a loose combination, which temporarily inhibits the functions of the cells. This theory only explains why these drugs have an affinity for nervous tissue. Since anæsthesia is a temporary state, it is likely that the action is physical rather than chemical, and there is evidence that changes in surface tension play a part. Lipoid affinity and surface affinity concentrate the anæsthetic on the cell membranes and alter the cellular permeability. Initially, anæsthetic drugs increase the permeability and this excites cellular activity; later the permeability is reduced and this seems to be the essential factor in promoting



narcosis. The effect may also be dependent on alteration of the electrical potential of the cell or of the intracellular catalase enzymes.

(b) *Respiratory system.* During the first stage, too strong an anæsthetic vapour may cause temporary inhibition of respiration reflexly from irritation of the fifth nerve endings; this is not usually troublesome, and careful administration will prevent it. In the second stage respiration is irregular during struggling, and, under careless administration, a series of deep breaths may produce a high concentration of chloroform in the blood and cause severe depression of the respiratory centre. In the third stage respiration is slow but shallow, because chloroform lowers the sensitiveness of the respiratory centre both to the sensory stimuli from the vagus and also to the chemical stimulus of the  $\text{CO}_2$  tension in the blood; the  $\text{CO}_2$  tension is also lowered owing to the quiescence of the body. The slowing becomes more pronounced as the anæsthetic is "pushed", till the breathing gradually ceases.

(c) *Circulatory system.* In the first stage, chloroform vapour may reflexly, through irritation of the fifth nerve, excite the vagus centre or render it more sensitive to external stimuli, so that slowing or temporary inhibition of the heart may occur; a previous injection of atropine, which paralyses the vagal endings, obviates this effect. Usually in the early stages of anæsthesia, the heart rate is accelerated owing to excitement, and blood pressure may rise from reflex stimulation of the vasomotor centre. In the later stages the heart is gradually slowed and weakened by direct muscular depression, especially of the auricle. The blood pressure falls, chiefly from direct relaxation of the arterial muscle, but chloroform also depresses the vasomotor centre and produces a reversal of the normal vasomotor reflex, whereby a sensory stimulus, instead of producing a rise in blood pressure causes it to fall.

*In light anæsthesia, two types of cardiac collapse may arise: (i) The sympathetic type occurs most frequently in nervous patients, whose blood already contains an excess of adrenaline. A sudden*

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increase in the concentration of the chloroform vapour weakens the heart muscle and also renders it highly sensitive to adrenaline. Commonly, some sensory stimulus, for example too early incision, is the exciting factor; this during light anaesthesia, causes a further output of adrenaline which may produce ventricular fibrillation. This immediately arrests the circulation, the blood pressure falls suddenly and after a few gasps respiration ceases. The only hopeful treatment is cardiac massage along with artificial respiration; injection of adrenaline is obviously contra-indicated. (ii) The *vagal type*, which may follow a sudden intake of concentrated chloroform vapour, and takes the form of inhibition of the heart due to stimulation (possibly reflex) of the vagus centre acting upon the already depressed and therefore sensitive cardiac muscle; the blood pressure falls rapidly and respiration gradually ceases; this type is not usually alarming as the heart escapes from vagus control, and it can be prevented or treated by an injection of atropine.

(d) *The pupil.* The pupil is dilated in the first and second stages reflexly from excitement. In the anaesthetic stage it is small; in the fourth stage it becomes widely dilated. Dilatation of the pupil, therefore, is a sign that the patient is having either too little or too much chloroform; in the former case (second stage) the dilated pupil reacts to light and often heralds a bout of vomiting; in the latter case (fourth stage) the widely dilated pupil does not react to light and is evidence of asphyxia.

(e) *The uterus.* The parturient uterus contracts freely in complete anaesthesia, with some loss of vigour and regularity.

3. DELAYED CHLOROFORM POISONING. This condition may arise gradually—when the patient never recovers thoroughly from the anaesthetic but becomes gradually prostrate, delirious and comatose; or suddenly—when, after apparent recovery, there develops, within 10 hours to 6 days, acute delirium alternating with periods of stupor and coma. There is commonly vomiting of blood, jaundice and haemorrhage from the bowel; bile secretion is reduced and bile pigments may appear in the urine; examina-

tion of the blood will show hypoglycæmia and a lowered alkali reserve; the urine contains acetone and diacetic acid and, post-mortem, the liver and other organs are found to be in a state of fatty degeneration. The condition is comparable with acute yellow atrophy and diabetic ketosis. Such cases occur most commonly in children or after prolonged anæsthesia. Excessive restriction of food, particularly carbohydrates, is a predisposing cause. Injections of dextrose, Ringer-lactate, or sodium bicarbonate assist in counteracting the ketosis.

4. **USES OF GENERAL ANÆSTHETICS.** General anæsthesia is employed: (i) In operations attended with pain. (ii) In operations where muscular contraction or spasm has to be overcome, reduction of herniæ, dislocations and fractures; catheterisation. (iii) In diagnostic manipulations, bimanual palpation of the pelvis. (iv) In conditions associated with excessive pain, especially the passage of biliary and renal calculus. (v) In parturition, the degree of anæsthesia induced being generally light so as not to inhibit reflex contractions of the abdominal muscles until the passage of the fetal head through the pelvis.

5. **METHOD OF ADMINISTRATION AND PRECAUTIONS NECESSARY FOR INDUCING ANÆSTHESIA.** This practical subject must be learned by experience and the student must interpret every symptom of pharmacological significance because only thus will he appreciate accurately the condition of the patient at any moment.

The following practical points can be discussed but briefly:

(i) *Selection of cases.* Chloroform must be given with great caution to the aged, to persons with myocardial weakness, to diabetic patients, to fat and anæmic persons, to epileptics and to chronic alcoholics. For such patients, nitrous oxide, ether or some other anæsthetic should be chosen. Operations on the mouth, nose or throat, with possible bleeding into the glottis, demand that the cough reflex should not be abolished.

(ii) *Preparation of the patient.* No food should be given for at least four hours before the operation. Artificial teeth should be removed. To allay excitement morphine with atropine or hyoscyne

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(to prevent salivation and cardiac inhibition) are usually injected prior to the induction of anaesthesia. This "premedication" also reduces the amount of anaesthetic necessary to maintain anaesthesia. The respiration and pulse should be carefully observed before allowing inhalation to begin.

(iii) *Selection of the anaesthetic.* The anaesthetic agents in general use at the present time are nitrous oxide, nitrous oxide with oxygen, diethyl ether, vinyl ether, cyclopropane, ethylene, trichloroethylene, and halothane. Chloroform, owing to its dangers, is generally avoided although convenient in some circumstances in general practice. Nitrous oxide with oxygen or ether is to be preferred unless there be some special reason to the contrary. Mixtures of several anaesthetics—such as the obsolete Alcohol-Chloroform-Ether combination have the disadvantage that the composition of the *inhaled vapour* varies with temperature and cannot be estimated. It is a common practice to start with a rapidly acting anaesthetic and to replace it, when unconsciousness has been achieved, by a more slowly acting one, for example nitrous oxide-ether sequence. The merits of ethylene, cyclopropane and trichloroethylene are described later.

(iv) *Selection of the apparatus.* Whilst elaborate inhalers are used in hospitals, simple apparatus may be equally safe, such as a piece of lint or flannel stretched over a wire frame, care being taken that with chloroform, the vapour is diluted freely with air. Apparatus for emergencies should include a cylinder containing carbon dioxide (5 per cent with oxygen), solutions of adrenaline, nor-adrenaline, methylamphetamine, nikethamide, atropine, hypodermic syringes, a pair of straight-tongue forceps and instruments for performing tracheotomy and laryngeal intubation.

(v) *Position of the patient.* The anaesthetist must accommodate himself to meet the convenience of the surgeon. If possible, the recumbent patient's head is so placed on a pillow that the saliva flows out of the mouth instead of into the stomach, and that the tongue does not fall back and produce dyspnoea. The respiratory movements of the chest and abdomen must not be restricted by clothes or bandages.

(vi) *Administration of chloroform.* The confidence of the patient should first be gained, whilst he is reassured and instructed how to breathe. When inhalation has begun, the anaesthetist must keep a

constant check upon the respiration, pupils and pulse (which is accessible in the temporal or facial arteries). Chloroform should be dropped slowly but steadily on the mask (from 10 to 50 drops per minute), the interval between the drops being gradually shortened. The pouring on the mask at intervals of a considerable quantity of chloroform must, above all, be avoided. The head should be tilted to the side and the lower jaw supported to prevent closure of the glottis. When the patient is anaesthetised, the condition should be maintained by the smallest possible amount of the drug (about 5-10 drops per minute). A lighter degree of anaesthesia is permissible during child-birth, but deep anaesthesia is necessary for rectal operations. The loss of the corneal and light reflexes, and stertorous breathing are generally employed as tests of insensibility, but reliance should not be placed upon a single sign.

(vii) *Complications and unfavourable symptoms.* Vomiting is generally preceded by pallor of the face and a few deep inspirations. Care must be taken, by affording a free exit, that nothing is drawn into the larynx; the head should be thrown more over to the side, and the mouth opened by pressure on the symphysis, or a gag may be inserted between the teeth. Tracheotomy may be necessary if vomited matter be inhaled.

Lividity of the face and prolonged deep stertor indicate lack of oxygen; the anaesthetic should be withheld and the patient allowed to breathe air. Mucus in the larynx may obstruct the free entrance of air.

Extreme pallor of the face is indicative of circulatory failure; the anaesthetic should be stopped, the head lowered and atropine injected.

Shallow breathing, especially if intermittent, calls for close attention; it may be due to lack of the  $\text{CO}_2$  stimulus or to severe depression of the centre. During anaesthesia, respiration may become shallow, or fail, from a train of circumstances, thus: overbreathing leads to excessive excretion of  $\text{CO}_2$  and, this being the normal stimulus to respiration, there follows a period of very shallow breathing (apapnia) to which the depressant action of the anaesthetic on the respiratory centre also contributes. It should be noted that the slow and shallow respiration of the third stage is due to the fact that the anaesthetic renders the respiratory centre less sensitive both to the afferent vagal stimuli and to the  $\text{CO}_2$  stimulus. Inhalations of carbon dioxide 5 per cent with oxygen will, however, increase the depth of respiration.

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(viii) *After-treatment.* Absolute quietness and keeping the eyes closed often prevent sickness after operation. Recovery may be hastened by stimulating deeper respiration by means of carbon dioxide inhalations. The room should be cleared of the anæsthetic vapour as quickly as possible. Food should not be given within 3 hours after the operation, and not even then unless the patient desires it; and for the first 12 hours should be cool, and consist chiefly of soups and jellies, milk being avoided. Chloroform sometimes causes albuminuria, and its use in diabetes mellitus is risky as it tends to produce ketosis.

(ix) *Excretion of chloroform.* Chloroform is excreted rapidly and almost wholly by the lungs. A small quantity is excreted in the urine and in the alimentary tract.

CHLOROFORM EXTERNALLY. Externally, if the vapour be confined or the chloroform rubbed into the skin, it acts as an irritant, causing redness with a sense of heat and pain, followed by anæsthesia due to depression of the sensory nerve endings of the part. A similar effect is produced on exposed mucous membranes. When given internally by the mouth, chloroform has a hot, sweet taste which renders it useful in pharmacy to cover the nauseous, bitter and astringent tastes of many drugs. Like alcohol, it causes reflex salivation; and in this way, as well as by a carminative and sedative action on the stomach, Chloroform Water and Spirit of Chloroform are useful adjuvants in mixtures prescribed for the relief of gastric discomfort and flatulence. In larger doses chloroform causes vomiting.

## ETHER

*Ether as a general anæsthetic.* Ether, when inhaled, is absorbed from the alveolar epithelium rapidly into the blood. Its action resembles that of chloroform and only the important differences between the two substances require to be mentioned here. These are:

1. Ether requires to be inhaled in high concentration (12-14 volumes per cent) in air for rapid induction and clinically about 6 per cent is used to maintain surgical anæsthesia. When time is allowed for equilibrium to be established, from 4 to 4.5 per cent

in air will maintain surgical anæsthesia while 7 to 8 per cent can produce respiratory failure. From 45 to 60 ml. are required to induce anæsthesia, and about 180 ml. per hour to maintain it. The blood and tissues in light anæsthesia contain about 0.1 per cent of ether, in surgical anæsthesia from 0.13 to 0.14 per cent, while respiratory depression occurs at 0.16 to 0.17 per cent. These figures show that the margin of safety with ether is greater than that with chloroform.

2. With ether the stage of excitement is more protracted; there is more struggling; the degree of anæsthesia is less profound; and muscular relaxation less complete. As ether is given with relatively less air, cyanosis is more common than with chloroform. Ether has only one-third the depressant action on the cerebrum, cord and medulla (respiratory centre) and is thus safer than chloroform.

3. Ether has only one twenty-fifth of chloroform's depressant action on the heart. In the stage of surgical anæsthesia, the pulse is usually quicker and fuller; the blood pressure is either normal or slightly increased particularly if the air supply is much reduced; the face is flushed from dilatation of the superficial vessels and bleeding is more profuse under ether. Cardiac syncope is very rare and, even when the respiration is failing from overdosage with ether, the pulse and blood pressure may be practically normal. Ether is therefore much the safer anæsthetic for cardiac cases.

4. Ether has a less pleasant odour and causes more irritation of the air-passages and more salivation than chloroform and is in general less acceptable to the patient. Local irritation in the upper respiratory tract and nasopharynx is greater with ether, because a higher concentration of ether is needed for induction; it should be noted that weight for weight chloroform is more irritant than is ether.

5. The after-effects of ether, in the form of sickness and bronchial catarrh or even pneumonia, are more common and severe than those of chloroform.

6. Ether convulsions of epileptiform type may occur during deep anæsthesia in young persons who are febrile as a result of infection; they are preceded by dyspnœa and cyanosis, and com-

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mence with twitching of the eyelids and facial muscles but soon spread over the body; they may be fatal. Their origin is obscure; they may occur with other anæsthetics. The anæsthetic must be stopped. Oxygen is not very helpful but thiopentone will control them if given early.

*Administration.* Ether may be given by means of a cone-mask or cone-shaped towel with a restricted air inlet, and by pouring 15 ml. of ether on the absorbent surface; or, like chloroform, by the open method, which avoids the sense of suffocation and cyanosis; but the ether requires to be dropped on at the rate of about 5-10 ml. per minute. Others prefer to give ether in closed inhalers with restricted air supply, which latter accounts for the flushing or cyanosis of the face and for the increased depth of respiration and full pulse. Ether anæsthesia can be induced rapidly by use of an inhaler with a rebreathing bag of 4-5 litres capacity, to which at first mixtures of 5-6 per cent  $\text{CO}_2$  in oxygen, to produce deep breathing, are added, and then ether, previously vaporised, in high concentration so as to raise the amount in the blood quickly to the anæsthetic percentage. By these means full anæsthesia is attained rapidly and the excitement stage almost eliminated; breathing is regulated by adding  $\text{CO}_2$  and  $\text{O}_2$  when required, while recovery is hastened by promoting deep breathing with this gaseous mixture.

In choosing between ether and chloroform, preference must be given to the safer anæsthetic, and therefore ether is very extensively used. In certain circumstances chloroform is preferable, such as for operations upon the mouth, because ether causes profuse secretion of ropy mucus; and in operations where a diathermy knife might come in contact with the ether vapour and ignite it. Infants bear chloroform better, and their delicate respiratory passages are less irritated by it than by the pungent vapour of ether; but chloroform is not to be regarded as a specially safe anæsthetic for children.

*Other Uses of Ether.* If ether is rubbed into the skin a rube-facient effect is produced, as with chloroform. Ether dissolves the sebaceous secretion; and in the form of Etheral Soap, it is a surgical detergent. Ether is used in Collodion to dissolve pyroxylin.



*Internally*, ether has a burning, disagreeable taste, and causes more local irritation in the mouth and reflex salivation than chloroform. In the stomach ether and the Spirit of Ether are irritants and local stimulants to the mucous membrane.<sup>4</sup> They relax spasmodic contractions and are therefore used as carminatives, relieving pain and facilitating eructation of gas. By irritation of the stomach they act reflexly upon the circulation and respiration, as rapidly diffusible reflex stimulants and spasmolytics. Preparations of ether might therefore be used as alternatives to ammoniacal "smelling salts" but such preparations are of greater interest to the first-aid worker than to the physician.

### VINYL ETHER

Vinyl Ether (Divinyl Ether) induces anæsthesia in one minute and, although causing some salivation, it does not irritate the air-passages nor impair circulation or respiration. Recovery takes place in about two minutes; vomiting is rare but there is a risk of liver damage if it is used for more than 1 hour. A mixture of vinyl ether 1 with ether 3 on an open mask induces anæsthesia rapidly and with adequate muscular relaxation for short operations, but the use of a closed inhaler with oxygen is preferable and, for longer operations, an absorbent for carbon dioxide is required. It is advocated for rapid inductions, short minor or dental operations, obstetrical practice and as a supplement to nitrous oxide and oxygen.

### ETHYL CHLORIDE

Ethyl Chloride is employed as a general anæsthetic for operations of short duration. It is administered from a closed inhaler; anæsthesia is induced in  $\frac{1}{2}$  - 1 minute, and lasts about  $1\frac{1}{4}$  minutes; recovery occurs in about 1 - 2 minutes. It may also be given by the open method, using 7 - 8 ml. for an adult. It is used in place of nitrous oxide for the removal of teeth, for brief operations, and prior to ether and chloroform administration as it shortens the period of induction. Ethyl chloride cannot compare with nitrous oxide in safety; it is a depressant to cardiac muscle, and headache and sickness are frequent after its use.

Sprayed on the skin, its low boiling point (12° C.) makes ethyl

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chloride a very rapid local anæsthetic by freezing. It is used for superficial surgical operations and for removal of front teeth. Care must be taken to avoid long application, which causes sloughing; thawing is painful.

### NITROUS OXIDE

Nitrous Oxide, being soluble about 1 in 2 of the plasma, is rapidly absorbed from the lungs and, if administered from an inhaler along with air, produces a stage of motor excitement—sometimes with hilarious laughter; the person behaves as if intoxicated, speech is confused, movements are unsteady and sensation is dulled.

Nitrous oxide acts as a depressant to the cerebral centres and is a general anæsthetic. If the undiluted gas be inhaled it produces a sensation of rumbling in the ears, mistiness of vision and of falling through space; within about a minute complete unconsciousness results with abolition of the sense of pain, loss of reflexes, but with incomplete muscular relaxation. When the patient is fully anæsthetised, the corneal reflex is absent but, owing to the deprivation of oxygen there are definite signs of asphyxia—facial cyanosis, slow and stertorous respiration, a slow and full pulse with raised blood pressure, dilated pupils and possibly some muscular twitching. On removing the mask these asphyxial symptoms quickly vanish; the anæsthesia lasts about 45 seconds and recovery is complete in from 1 to 3 minutes; after-effects are very rarely experienced.

Pure Nitrous Oxide is used very largely as an anæsthetic in dentistry to permit painless extraction of teeth and for minor surgical operations. The average amount required is from 10 to 15 litres. It is also employed as a preliminary to ether anæsthesia, and the "Gas-Ether Sequence" is an excellent method for major operations, as it induces rapid anæsthesia without a stage of excitement. Operations requiring several minutes may be performed by allowing intermittently—about 1 in 5—a breath of air. Although pure nitrous oxide gas is an extremely safe anæsthetic, it should not be used for patients having a high blood pressure or serious cardiac lesions.

## DILLING'S CLINICAL PHARMACOLOGY

*Mixtures of nitrous oxide and oxygen* are used to enable more prolonged operations to be performed without asphyxial symptoms. Special apparatus is used so that the gases may be mixed in any proportion. Induction is carried out by pure nitrous oxide, or with the addition of 2 per cent of oxygen, and then the percentage of oxygen is increased until cyanosis is eliminated, which occurs usually with a mixture of 90 per cent nitrous oxide and 10 per cent of oxygen; but as the proportions vary between 5 and 15 per cent of oxygen they require to be carefully balanced.

Under nitrous oxide and oxygen anaesthesia breathing is slow, regular and snoring, the pulse more rapid and the blood pressure somewhat increased; and, although the reflexes are almost abolished, the muscular relaxation is not complete. This method is, however, the safest anaesthetic method except for major operations, when ether may be used as a supplementary anaesthetic.

### ETHYLENE

A mixture of ethylene 90 per cent with oxygen 10 per cent induces surgical anaesthesia almost (3-5 minutes) as rapidly as, and more effectively than, nitrous oxide, without causing cyanosis, dyspnoea or rise of blood pressure but providing fairly complete muscular relaxation. When anaesthesia is established, it can be maintained by a mixture of 80 per cent ethylene and 20 per cent oxygen. In ethylene anaesthesia, respiration is regular but somewhat slow; there is an absence of pulmonary irritation or salivation and the pulse remains about normal. Recovery occurs very rapidly in from 2 to 5 minutes but vomiting is a frequent sequel. Experience indicates that ethylene gives a better surgical anaesthesia than nitrous oxide and oxygen and without the objectionable effects of ether.

### CYCLOPROPANE

Cyclopropane induces anaesthesia rapidly without causing local irritation. Percentages of 7.5 to 10 will maintain light anaesthesia, and of 15 to 20 per cent deep anaesthesia with good muscular relaxation; and 42 per cent will produce respiratory arrest. As the gas is expensive, it is usually given along with pure oxygen

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by using a carbon dioxide absorption technique. Recovery is rapid and after-effects uncommon, but during deep anaesthesia watch must be kept for failing respiration and for a rapid and irregular or very slow pulse, all of which are danger signals. Cyclopropane has proved very valuable for major thoracic and abdominal operations, and for patients with pulmonary infections, heart disease or shock. Its advantages are that it is not irritant, and when used with a high percentage of oxygen it induces quiet breathing. Its disadvantages are that it causes capillary oozing and may produce postoperative collapse with low blood pressure (cyclopropane shock). As cyclopropane has no irritant action on the respiratory tract, induction is exceptionally smooth, and these circumstances create the danger of serious overdose: the patient rapidly enters the fourth stage of anaesthesia unless expert supervision is maintained.

### TRICHLOROETHYLENE

Trichloroethylene is a general anaesthetic which is pleasant to inhale, and rapidly induces in the first stage general analgesia without irritant effects or increased salivary or bronchial secretion. On the other hand early cardiac arrhythmia is fairly common; occasionally second-stage excitement occurs with panting respiration; in the stage of surgical anaesthesia, abdominal muscular relaxation is incomplete; and the pulse and respiration are commonly increased in rate. The skin vessels are not dilated, hence capillary oozing does not occur as with ether or cyclopropane. After-effects which include headache, mental confusion, nausea and vomiting, are common but usually slight.

Trichloroethylene is not sufficiently volatile for open-mask administration; it can be inhaled in sufficient concentration to induce general anaesthesia from the bottle of a "draw over" apparatus and, by regulated partial rebreathing, surgical anaesthesia can be maintained with about 13 ml. per hour. It is used mainly as an adjuvant to gas and oxygen anaesthesia. It must not be used by the soda-lime closed-circuit technique because the heat decomposes it into dichloroacetylene which causes paralytic complications.

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Trichloroethylene is indicated for minor surgery, for operations involving diathermy, for example in thoracic surgery and in superficial operations, to obviate excessive bleeding. Inhalers, designed for self-administration by patients, for example during childbirth, are available.

### HALOTHANE

Halothane ("Fluothane") is a fluorinated hydrocarbon. It is a clear, colourless fluid: Sp. gr. 1.862; BP 50.2° C. Its odour is not unpleasant and resembles that of chloroform. Experimental work on animals has shown halothane to be about five times more powerful than diethyl ether. It produces smooth induction when a 2 per cent vapour is inhaled; there is little irritation of the respiratory tract. Anaesthesia is maintained by using concentrations of about 1 per cent. Special delivery apparatus is needed to provide precise control of dosage: this means that the use of halothane is virtually impossible except in hospitals and by experienced anaesthetists. Further, the status of halothane in clinical practice is still unsettled. Its toxic effects include respiratory depression; arterial hypotension—proportional to the depth of anaesthesia, and probably attributable to depression of central vasomotor mechanisms; bradycardia and occasionally cardiac arrhythmias. The use of adrenaline is strictly contra-indicated during halothane anaesthesia, as it is particularly liable to cause serious cardiac irregularities. The depressant effect of halothane on heart-lung preparations has been shown to be about 70 per cent. of that caused by chloroform. Halothane potentiates the action of *d*-tubocurarine and especially the ganglion-blocking effect of the relaxant: this has sometimes caused profound fall of blood pressure during surgical operation. Again, the use of an anticholinesterase such as neostigmine during halothane anaesthesia has been found to be dangerous because of an enhanced cardio-inhibitory action with consequent risk of cardiac arrest.

This brief reference to the properties of this new general anaesthetic may serve to emphasise some of the points made in the introductory section of this chapter. Halothane is a drug which has many outstanding advantages, but they depend upon the services of expert anaesthetists equipped with special apparatus. Again,

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the useful concentration of halothane is also a critical one: if excessive amounts are given, the anaesthetist is likely to become more pre-occupied with the alarming side-effects of the drug than with its virtues at optimum concentrations. Lastly, now that the practice of anaesthesia embraces the use of muscular relaxants, ganglion-blocking agents, and a great many drugs that affect the functioning of the autonomic nervous system, it clearly emerges that the assessment of a new general anaesthetic calls for prolonged and detailed study. This applies to the use of halothane: it was introduced in 1956, but, after three years, it is still too early to say whether modern technical procedures will ensure for it a permanent place among anaesthetics.

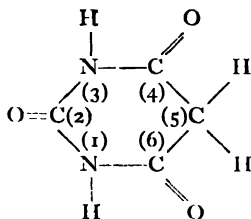
## ORGANIC HYPNOTICS

A hypnotic drug is one which produces sleep resembling natural sleep. Although hypnotics are very numerous they can be easily classified. This lends itself to the procedure adopted by the medical practitioner who inevitably uses only a small selection of the drugs that are available: he finds it convenient to consider a hypnotic in terms of what would be *ideal* for clinical practice. Is it convenient to take, reliable and harmless? Is its use free from after-effects, habituation and the danger of addiction? Some of the characteristics of hypnotics can be forecast from a consideration of chemical structure, but generalisations are often fallacious; and from the doctor's viewpoint the only reliable assessment is that derived from well-designed clinical trials. A general rule which applies to so many other groups of drugs is certainly relevant to hypnotics: the individual practitioner must make a judicious selection from the drugs available; the range of therapeutic effects depends more on the practitioner's judgment and his knowledge of medicine than on the complexity and novelty of the drugs at his disposal.

### BARBITURATES

These are derivatives of barbituric acid, which is prepared by the chemical combination of urea and malonic acid. The chemical formula of barbituric acid is shown below:

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It has no hypnotic effect, but on replacing the two hydrogen atoms of the carbon atom in position 5 of the ring by alkyl (e.g. ethyl) or aryl (e.g. phenyl) groups, many cerebral depressants have been obtained. If ethyl groups are substituted for these H atoms, barbitone ("Veronal") is produced. Phenobarbitone is 5-phenyl-5-ethylbarbituric acid. Other radicals may be substituted at either of these hydrogen atoms and also at one or both of the nitrogens. The nature of the side-chain greatly influences the duration of action of the compound: in general the longer the side-chain the shorter is the action—because the long side-chain is liable to be broken down quickly by metabolic processes. A different series of compounds known as the thiobarbiturates (e.g. thiopentone) is obtained by replacing the oxygen atom on the carbon atom in position 2 by a sulphur atom; these are destroyed very rapidly in the body.

A single chemical substance, e.g. a barbiturate, may have a dozen different trade-names. Further, phenobarbitone may be compounded with other substances and thus there are scores of pharmaceutical preparations—each with its trade name—containing these hypnotics. In order to avoid confusion it is therefore strongly recommended that only the official names be employed. The barbiturates in common use are listed on p. 220.

**PHARMACOLOGY.** The barbiturates have a depressant action at all levels in the central nervous system. The cerebral cortex and the reticular activating system are the most sensitive to their action. The cerebellar, vestibular and spinal-cord systems are less sensitive, and the vital centres in the medulla the least sensitive of all. The barbiturates raise the threshold of excitability for neurons by stabilising the cell membrane and prolonging the

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recovery time after stimulation. The mechanism by which these changes are accomplished is unknown. By altering the dose of barbiturate, any degree of depression can be obtained from mere tranquility to deep coma. The direct action on other organs is negligible in hypnotic doses; the effects are those accompanying sleep. The pharmacological actions of the barbiturates are basically similar but phenobarbitone has a specific depressant influence on the motor areas of the cerebral cortex, making it a valuable drug in the therapy of major epilepsy ("grand mal"). In hypnotic doses, the barbiturates have no analgesic action, and indeed if they are prescribed alone in painful conditions they may cause excitement, restlessness and delirium. Given with an analgesic, the actions of the drugs are synergistic. Barbiturates also increase the action of ethyl alcohol, and this may be a matter of considerable practical importance.

**CLASSIFICATION.** The most useful classification of the barbiturates is based on the duration of their hypnotic action. This divides them into four groups, according as the action is long, intermediate, short or very short (p. 220). These differences are related to the rate of detoxication by the tissues (mainly the liver), the rate of excretion in the urine and the constitution of the side-chains. *Absorption* of the barbiturates from the intestine and after intramuscular injection is rapid; and the compounds are distributed to all tissues of the body, freely crossing the placental barrier. Bone and muscle usually contain the least barbiturate; brain, liver and kidney show higher concentrations. Equilibration between brain and plasma may be slow for some barbiturates. In the cerebrospinal fluid the concentration of thiopentone is high, but that of the other barbiturates is low. Serial analyses of plasma and body fat after intravenous injection of small single doses of thiopentone show a rapid transfer of the drug from plasma to the fat; this explains the very transient action of such doses. The body has two principal methods of disposing of the barbiturates: they may be either detoxicated in the liver by side-chain oxidation, or excreted by the kidney. The speed of disposal determines the duration of action of the particular barbiturate. Phenobarbitone and barbitone are mainly excreted by the kidney. About 50 per



cent of phenobarbitone is cleared in 8-12 hours, but only 20 per cent of barbitone is found in the urine within 24 hours of its administration; traces of barbitone can still be found after 7 days. It is therefore important to know the state of renal function before prescribing these two barbiturates. The other barbiturates are mainly detoxicated in the liver and should be prescribed with care in patients with hepatic insufficiency.

*Tolerance* to barbiturates does occur, but not to a degree which notably affects ordinary therapeutic use. *Psychic dependence* is common in patients who are mentally unstable and withdrawal of the drug leads to craving and insomnia. The continued use of barbiturates can produce addiction in some patients, with a characteristic withdrawal syndrome manifesting physical abnormalities. The abstinence syndrome varies from patient to patient: some complain only of weakness and malaise: others develop convulsions and delirium. Tremor, abdominal cramps, nausea, vomiting and postural hypotension may occur. Loss of weight may be rapid. The treatment of the barbiturate addict consists in withdrawing the drug gradually under careful medical and psychiatric surveillance.

*Idiosyncrasy* to the barbiturates may be inborn. More often idiosyncratic reactions have an allergic basis: they are likely to occur in patients who have a history of asthma, urticaria and such conditions. The chief signs are puffiness of the eyelids, lips or face, and erythema, urticaria or even dermatitis. Drug fever may occur. Rarely phenobarbitone has been reported to cause exfoliative dermatitis. Exceptionally, joint pains may necessitate withdrawal of the drug. In strange or disturbing surroundings barbiturates given to children or to old people may cause mental confusion or even excitement.

Neurotic patients with a low threshold for discomfort of any kind may complain of a prolonged headache, vertigo and lassitude.

*Contra-indications* to the use of the barbiturates are recognised. When severe impairment of renal function is present, barbitone or phenobarbitone should not be prescribed; in patients with

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severe upset of hepatic function, the short-acting barbiturates (which are eliminated by the liver) should be used with caution. Only small doses—and preferably of the slow-acting preparations—should be given in cases of advanced cardiac disease, in the aged, in severe toxæmia, or where there is severe respiratory insufficiency. Idiosyncrasy constitutes a clear contra-indication, and this should be remembered in those with a history of allergic disorders.

*Routes of Administration.* The oral route should be employed whenever possible, and parenteral administration is indicated only when the patient is vomiting, or cannot swallow, or when rapid onset of the depressant action is necessary. When a rapid effect is required the sodium salts of the barbiturates, e.g. sodium phenobarbitone, may be given intramuscularly. The thio-barbiturates should not be given hypodermically. Intravenous therapy is dangerous and requires expert supervision; it is utilised in the production of anaesthesia by thiopentone or, less commonly, hexobarbitone.

When choosing a barbiturate for a particular patient, the most suitable drug is that which is most rapidly eliminated, consistent with the patient's requirements. Thus, where insomnia consists only in difficulty in falling asleep—with undisturbed sleep thereafter—the appropriate drug is usually a short-acting one such as pentobarbitone.

The four groups of the barbiturates, classified by the duration of their hypnotic action, can now be considered.

**1. LONG-ACTING BARBITURATES.** Although it is possible to use barbitone and also phenobarbitone (and their soluble sodium salts) as hypnotics, the practice is obsolete. Barbitone has for many years been superseded by other barbiturates which are incomparably better hypnotics for clinical use. Again, Phenobarbitone, though capable of causing drowsiness and—in excessive doses—deep sleep, is far from being the hypnotic of choice: in small doses it acts as a useful sedative in combating anxiety, and in larger doses it is a valuable depressant of the motor cortex and therefore specially useful in the management of

epilepsy (p. 227). Sodium Phenobarbitone injected intramuscularly or intravenously (0.2 G.) produces a fairly sudden and intense sedative action which is useful when dealing with excited patients, or those in status asthmaticus or status epilepticus. Barbitone is no longer included in the BP.

2. INTERMEDIATE-ACTING BARBITURATES. Their hypnotic action begins in about half an hour and lasts for 4 to 8 hours. There are no after-effects. These drugs should be given at a suitable time—say 11 p.m.—to take advantage of the natural tendency to sleep at this hour. It is highly important that the patient should be fasting when he receives the hypnotic: the presence of food in the stomach delays the onset of the pharmacological action and the effect is also diminished in its intensity. Absorption is rapid, as also is their inactivation in the liver. Amylobarbitone ("Amytal"), Allobarbitone ("Dial"), Butobarbitone ("Soneryl") and Pentobarbitone Sodium ("Nembutal") are all members of this group. In a dose of 0.1-0.2 G. pentobarbitone sodium is a valuable hypnotic for patients who have difficulty in getting off to sleep; it is also used as a basal anaesthetic and before childbirth. Pentobarbitone sodium may also be given intravenously in doses of 0.2-0.5 G. in 10 ml. of sterile water to alleviate convulsions, or in maniacal excitement.

3. SHORT-ACTING BARBITURATES. These act as hypnotics in from a quarter to half an hour and sleep lasts for 3 to 6 hours without after-drowsiness. Quinalbarbitone Sodium ("Seconal") and Cyclobarbitone ("Phanodorm") are in this group. The hypnotic dose of each of those drugs is 0.1-0.2 G.

There are many diseases in which it is desirable to produce a sustained mild cerebral depression without inducing sleep. Such maladies include conditions in which anxiety or excessive nervous tension may require relief: for example, arterial hypertension, hyperthyroidism, dyspepsia and menopausal symptoms. Barbiturates of the above three groups in repeated sub-hypnotic doses are valuable in such patients. Doses of about one-quarter of the hypnotic dose are used to produce the desired *sedative* action. Phenobarbitone, 30 mg. three times a day, is usually

to be preferred for this purpose because of its long duration of action.

4. VERY SHORT-ACTING BARBITURATES. When used as hypnotics, these act in about 15 minutes, but they are rapidly detoxicated in the liver and sleep will last for only 1-2 hours. The oral dose of Hexobarbitone ("Evipan") is 0.25-0.50 G. Injection of Hexobarbitone Sodium can also be used as an intravenous anæsthetic, but Thiopentone Sodium ("Pentothal") is most frequently employed as the intravenous anæsthetic of choice; the dose of thiopentone sodium is 0.1-0.5 G. given intravenously. It is supplied as a yellowish-white, soluble powder in an ampoule, and is dissolved in 20 ml. of sterile water immediately prior to injection as a 2.5 per cent solution. The technique of intravenous anæsthesia demands a competent and experienced anæsthetist, but the general principles of the method may be discussed here. Care must be taken to avoid intra-arterial injection or extravasation of thiopentone sodium subcutaneously as the solution is an irritant and causes local sloughing. The injection must be administered slowly, with fractional doses given at intervals sufficiently long to allow assessment of the effects. It is impossible to predict how much thiopentone sodium will be required to produce anæsthesia in the individual patient. The signs characteristic of the induction phase in inhalation-anæsthesia are not observed and the patient appears to "fall asleep" quite suddenly during the course of the injection. The stage of surgical anæsthesia is heralded by diminution or loss of superficial and tendon reflexes, normal or constricted pupils, falling backwards of the tongue, shallow respiration and a fall in blood pressure. Abdominal relaxation may be inadequate even in deep anæsthesia. If in an adult 0.5 G. of thiopentone sodium is injected in this way, the anæsthesia will usually last for about 15 minutes. When a longer period of anæsthesia is needed, additional doses of 0.05-0.1 G. given every 5 or more minutes will maintain anæsthesia: not more than 1.5 G. should be given as the total dose. The rate of recovery from thiopentone sodium is variable, but is usually proportional to the total amount of the drug used. The chief advantages of the intravenous barbiturates are that induction is rapid and quiet with no excitement, holding

of the breath or respiratory irritation; it is rapidly eliminated and recovery is therefore speedy. Administration which is too rapid may cause a marked fall in blood pressure; laryngospasm may occur during induction and overdosage produces severe depression of respiration and the vasomotor mechanisms. Patency of the airway should be maintained at all times during intravenous barbiturate administration; the insertion of an endotracheal tube prevents upper respiratory obstruction.

Barbiturates are used in obstetrics to produce relaxation and amnesia during labour. The barbiturate is generally given in conjunction with other sedatives and the method requires constant skilled supervision. The newborn infant is liable to show delay in the onset of breathing because of respiratory depression.

A further interesting and valuable action of the barbiturates is found in their ability to prevent or abolish the convulsions which are caused by cocaine or one of its substitutes. A prophylactic dose of barbiturate is given orally about an hour before the injection of the local anaesthetic, e.g. 0.1-0.2 G. of pentobarbitone sodium or 0.12 G. of phenobarbitone sodium. Should convulsions occur, the treatment is by intravenous injection of a barbiturate.

#### BARBITURATE POISONING

*Chronic.* The symptoms and signs are those of widespread intoxication of the tissues of the nervous system. Inevitably there is evidence of deterioration of intellectual acuity, weakening of motor functions, disorganisation of autonomic activities—especially in the mid-brain, and gross disturbance of cerebellar control of coordination. In passing it may be pointed out that although drug therapy and nutritional disturbances often result in adverse effects which are curiously selective in their impact on the organism—even to the extent that they are regarded as “characteristic”—a viscus (or specialised cells within it) must declare the abnormality in *quantitative* terms: the normal activities of the tissues are either increased or decreased; and of course there is the third possibility—that changes have occurred in the cytoplasm or in the body fluids, but not to an extent which becomes apparent in terms of symptoms and signs.

The usual effects of chronic intoxication from prolonged

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medication are apathy, loss of the power of concentration and somnolence; these are sometimes accompanied by other signs such as vertigo, muscle weakness or incoordination, squint, dysarthria and tremor. The tendon reflexes may be exaggerated or diminished and the plantar responses may be extensor. The urine may show albumin and casts.

*Acute.* This may result from accidental overdose or from suicidal intent. There is prolonged deep coma with respiratory depression, low blood pressure and oliguria. The muscles are flaccid, the tendon reflexes diminished or absent, and the plantar responses may be extensor. The respiratory depression may take various forms: the breathing may be slow, or periodic breathing may be present and finally it is rapid and shallow. Death is due to respiratory failure, which may occur suddenly and unexpectedly. The range of fatal doses reported is very wide; for example, in the case of phenobarbitone 4-6 G. orally is usually fatal, but a patient has recovered from a dose of 9.3 G. In general, absorption of 5 to 10 times the full hypnotic dose is likely to cause serious poisoning.

The treatment of chronic overdosage with barbiturates is the same as that for addiction to the drug. In the case of barbiturate coma due to acute poisoning, the objectives of therapy are to remove unabsorbed poison from the intestinal tract by gentle but thorough gastric lavage, counteract the depressant effects of the barbiturate on the central nervous system by means of cerebral stimulants (see p. 179) and prevent the onset of complications. Competent nursing care is essential.

### CHLORAL HYDRATE

Chloral Hydrate is a chlorinated derivative of ethyl alcohol. It is a powerful and reliable hypnotic. Introduced to medicine in 1869, it is the oldest of the hypnotic group and remains one of the best. Chloral hydrate is irritant to the stomach and should be given in dilute solution flavoured with, for example, orange squash or syrup of ginger. It is rapidly absorbed from the intestine and is largely reduced in the body to trichloroethanol, itself a powerful hypnotic. A portion of this alcohol is then combined, in the liver

mainly, with glycuronic acid to form urochloralic acid which is inert. Chloral is excreted mainly by the kidneys as urochloralic acid and in combination with sulphuric acid.

In therapeutic doses, chloral hydrate acts as a rapid and powerful hypnotic by depressing the psychical and perceptive centres of the cerebrum; the intellect becomes less active and less responsive to external impressions. In 15 to 30 minutes it produces drowsiness which is followed by natural refreshing sleep lasting from 6 to 8 hours. During sleep the pulse and respiration are slower than normal and the pupils are contracted, but the reflexes are not affected. Pain is not relieved; the patient can be roused by sensory stimulation. If the patient is roused prematurely, mental confusion and drowsiness may be apparent, and he may complain of headache. All but the mildest hypnotics produce similar effects. Rarely, brief excitement precedes the hypnotic action.

Large doses (more than 2 G.) produce deep prolonged sleep in which, from depression of the cerebral sensory and motor areas and even involvement of the spinal cord, pain is dulled and the reflexes are less active. Toxic doses produce deep coma associated with anaesthesia, abolition of reflexes, muscular relaxation and depression of the medullary centres. The blood pressure falls, respiration becomes slow and shallow, and death results from paralysis of the respiratory centre.

*Circulatory System.* This is not significantly affected by hypnotic doses, although the blood pressure may fall slightly due to muscular inactivity and peripheral vasodilatation secondary to mild depression of the vasomotor centre in the medulla. Unfavorable effects on the heart only occur after very large doses of chloral hydrate and there is no evidence that repeated administration of the drug in hypnotic doses has a deleterious effect on the heart.

Repeated administration of chloral hydrate produces tolerance and in nervous patients may lead to the establishment of a drug habit. Chronic poisoning with chloral hydrate may lead to fatty degeneration of the liver, kidney and other internal organs.

Chloral hydrate is very soluble in water and is prescribed as a draught for oral administration in a dose of 0.3-2 G.

### CHLORBUTOL ("Chloretone")

Chlorbutol is slower and less reliable as a hypnotic than chloral hydrate, but it does not irritate the stomach. It may be used in mild cases of nervous insomnia in a dose of 0.3-1.2 G. It is credited with a mild anæsthetic effect on the gastric mucosa and for this reason it was formerly a standard remedy for travel sickness; hyoscine and the antihistamines have made this use of chlorbutol obsolete.

### PARALDEHYDE

Paraldehyde is a polymer of acetaldehyde. It is a colourless, transparent, inflammable liquid with a characteristic pungent odour and a burning acrid taste. In sunlight it decomposes to acetaldehyde and should be stored in dark amber-coloured glass containers. Following oral administration of the ordinary hypnotic dose, 2-8 ml., paraldehyde is rapidly absorbed and induces, in 15 minutes, a light sleep resembling natural sleep and lasting 6-8 hours without subsequent drowsiness. Rarely it causes preliminary excitement. The hypnotic action is not so powerful as that of chloral hydrate and like that drug, *therapeutic doses* of paraldehyde have no significant effect on the cardio-respiratory function. Toxic doses cause death by depression of the respiratory and vasomotor centres in the medulla. Paraldehyde is more effective than chloral hydrate in raising the threshold for electro-shock convulsions in animals; this experimental observation is in keeping with its proved therapeutic value as an anticonvulsant. Habituation to paraldehyde occurs rarely.

After absorption, about 80 per cent of the drug is destroyed in the body, the remainder being excreted through the lungs and kidneys. The principal site of inactivation is probably the liver, and paraldehyde should not be prescribed in the presence of severe parenchymatous hepatic disease. Objections to its use are the unpleasant taste, its excretion in the breath (which may be objectionable to the patient's attendants) and its tendency to cause gastric disturbance unless well diluted.

Paraldehyde is ordinarily given by mouth, in a dose of 2-8 ml., but it can be injected intramuscularly. It is a safe hypnotic for use



in asthma, in the insomnia of cardiac or respiratory diseases and in debilitated patients. In an emergency, when the anticonvulsant effect is desired, it can be injected slowly intravenously, diluted at least tenfold with physiological saline. As a basal anæsthetic paraldehyde is given rectally  $1\frac{1}{2}$  hours before operation in 10 times its own volume of physiological saline. The dose of paraldehyde as a basal anæsthetic is 4 ml. per stone of body weight; the total dose must not exceed 30 ml.

#### AMYLENE HYDRATE

Amylene Hydrate, (Tertiary Amyl Alcohol) ranks between chloral hydrate and paraldehyde as a hypnotic. It induces in about 20 minutes sleep which lasts about 6 hours. It is a clear volatile liquid, the hypnotic dose of which is 2-4 ml. but is principally used as the solvent for tribromoethylalcohol ("Bromethol") which is a basal anæsthetic (p. 189).

There are other groups of hypnotics which are now regarded as obsolete, either because of their toxicity, e.g. sulphonal, or because the hypnotic action is weak, e.g. urethane.

#### THE SULPHONE GROUP

The action of these hypnotics depends on the presence of alkyl radicals united to the disulphone group.

**SULPHONAL.** Sulphonal is a tasteless almost insoluble substance which is very slowly absorbed after oral administration. From 4 to 5 hours after a hypnotic dose of 0.3-1.2 G. it produces sleep which lasts for 10-12 hours. On waking there is a marked and protracted drowsiness, because sulphonal is very slowly excreted during the 48 hours following a single dose. If sulphonal is given on consecutive days symptoms of overdose develop because there is cumulation: excretion does not keep pace with intake of the drug; these are headache, confusion, abdominal pain, vomiting and diarrhœa, muscle weakness or cramps; urticarial skin rashes are also common. Methæmoglobinæmia and hæmatoporphyrinuria may occur.

Sulphonal is now rarely prescribed, because of its toxicity.

**Methylsulphonal.** Methylsulphonal is a more powerful and rapid hypnotic than sulphonal but it may induce the same toxic symptoms.

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### THE UREA GROUP

These are derivatives of urea or carbamic acid. The hypnotic powers of these ureides vary with the number of alkyl radicals they contain.

*Urethane.* This mono-ureide is a mild and unreliable hypnotic in doses of 1-2 G. Although it is no longer used as a hypnotic it has important actions in patients suffering from chronic myeloid leukaemia (p. 597).

**CARBROMAL.** Carbromal is a useful sedative and mild hypnotic, acting in 30 minutes and producing no after-effects. The dose is 0.3-1 G.

**BROMVALESTONE** ("Bromural"). In a dose of 0.3-0.6 G. bromvaletone is a useful mild hypnotic producing sleep which lasts for about 4 hours. Carbromal and bromvaletone are combined in the proprietary preparation "Persomnia".

**FEWER HYPNOTICS** (other than Barbiturates). There have become available in recent years two synthetic non-barbiturate hypnotics which are widely used. These are methyprylone and glutethimide.

**METHYPRYLONE** ("Noludar"). Methyprylone is a compound of the piperidine series which produces in  $\frac{1}{2}$ -1 hour sleep lasting for about 6 hours. With this hypnotic dose of 200-400 mg. there is no depression of respiration or of the cardiovascular system. It does not cause gastric irritation. Methyprylone has not been reported to cause tolerance, habituation or drug idiosyncrasy, but until this drug has been used more extensively in medical practice it would be premature to say that such effects do not occur.

Methyprylone may also be prescribed as a sedative in a dose of 50 mg. thrice daily.

**GLUTETHIMIDE** ("Doriden"). Glutethimide ( $\alpha$ -phenyl- $\alpha$ -ethyl glutarimide) produces sleep which lasts for about 6 hours. No undesirable side-effects have yet been reported following on its oral administration in a dose of 0.5 G.

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## *Names of Commonly Used Barbiturates*

<i>Name</i>	<i>Other Names</i>	<i>Dose: Milligrams</i>
Phenobarbitone	Luminal	30 120
Phenobarbitone Sodium	Luminal Sodium	
Injection of Phenobarbitone Sodium		
Methylphenobarbitone	Prominal	60-200
Barbitone	Veronal	300-600
Barbitone Sodium	Medinal	
Amylobarbitone	Amytal	100-200
Amylobarbitone Sodium	Amytal Sodium	100 200
Butobarbitone	Soneryl	100 200
Allobarbitone	Dial	30 200
Pentobarbitone Sodium	Nembutal	100 200
Quinalbarbitone	Seconal	100-200
Cyclobarbitone	Phanodorm	100 200
Hexobarbitone	Evipan	250-500
Hexobarbitone Sodium		200-1,000
Thiopentone Sodium	Pentothal Sodium	100 500

## *Classification of Barbiturates by Duration of Action*

<i>Name</i>	<i>Duration of Action (hours approx)</i>	<i>Route</i>
Phenobarbitone	Long: 8-16	Oral
Phenobarbitone Sodium	Long: 8-16	Oral or intramuscular or intravenous
Barbitone	Long: 8-16	Oral
Amylobarbitone	Medium: 4-8	Oral
Amylobarbitone Sodium	Medium: 4-8	Oral
Butobarbitone	Medium: 4-8	Oral
Allobarbitone	Medium: 4-8	Oral
Pentobarbitone Sodium	Medium: 4-8	Oral
Quinalbarbitone	Short: 3-6	Oral
Cyclobarbitone	Short: 3-6	Oral
Hexobarbitone	Very Short: 1-1	Oral, rectal, intravenous, intramuscular
Thiopentone Sodium	Very Short: 1-1	Intravenous

## TRANQUILLISERS

These drugs are reputed to produce changes in "emotional tone", and thus relieve anxiety and mental tension. It is claimed that this is achieved without causing drowsiness or impairment of efficiency. Within recent years, many such tranquillisers have been produced for the treatment of patients with anxiety neurosis and minor functional disturbances, as well as for patients suffering from psychotic diseases. Therapeutic evaluation of these drugs is difficult: much of this work must be done with animals, and in the specialised psychological tests that are used, many include the cultivation of a conditioned reflex to a noxious stimulus. The site of action and the mode of action of the tranquillisers are also difficult to define, as we know very little about the cellular metabolism of the brain in its relationship to thought and the state loosely described as emotional tension.

The tranquillisers can be placed in two main groups roughly corresponding to their main use in psychiatric states. The first comprises the drugs used predominantly in the psychoses and includes reserpine (p. 706), chlorpromazine and their congeners; the second group includes drugs which are more effective in the anxiety neuroses and minor functional disturbances.

Reserpine, an alkaloid of *Rauwolfia serpentina* (p. 318) is commonly used as a hypotensive agent. It is an effective tranquilliser in the treatment of some of the organic psychoses such as schizophrenia, toxic confusional states and delirium tremens, senile and presenile dementia. The mechanism of the tranquillising effect of reserpine is obscure, mainly as our knowledge of biochemical changes associated with thought and emotion is so scanty. There is, however, evidence that reserpine-like substances interfere with the retention in brain tissue of 5-hydroxytryptamine (serotonin) and the catechol amines; and reserpine also blocks the action of serotonin. Lysergic acid diethylamide (LSD) is a drug which can produce hallucinations and disturbances of mood; this drug is antagonised by serotonin. The relationship between these substances and disturbance of mood or behaviour in man is purely speculative and it may be that in the future other bio-

① *Reserpine* .  
 ② *Chlorpromazine* (Largactil)  
 ③ *Meprobamate* (Meprofen)  
 ④ *Phenothiazine hydrochloride* (Ritalin)  
 ⑤ *Phenothiazine* (Largactil)  
 ⑥ *Phenothiazine* (Largactil)

chemical cellular processes will be shown to be altered by reserpine and related compounds in their tranquillising effect. The toxic effects of reserpine, which include Parkinsonism, are noted on p. 318. Of the alkaloids of rauwolfia, reserpine has been the one in common use, but it is likely that rescinnamine will prove to be a more potent tranquilliser. The oral dose of reserpine or rescinnamine is 1-15 mg. and the most effective tranquillising dose for the individual patient is that which just falls short of producing the signs of Parkinsonism.

### (*Chlorazone*) CHLORPROMAZINE

Chlorpromazine ("Largactil") is 10-( $\gamma$ -dimethylaminopropyl)-2-chlorophenothiazine. It is closely related chemically to the antihistamine drug, promethazine (p. 286). Chlorpromazine has no significant antihistaminic action. It is a white powder soluble in water and is light-sensitive. Chlorpromazine is known to be a potent inhibitor of many enzymatic processes and this may explain its many and varied pharmacological actions. It has gangliolytic, adrenolytic, antipyretic, sedative and anti-emetic properties; it also enhances the action of many analgesic drugs and some central depressant drugs. The anti-emetic action is on the chemoreceptor trigger zone for vomiting situated in the medulla. A dose of chlorpromazine slightly less than that which produces drowsiness prevents vomiting induced by many agents which act through this trigger zone. Chlorpromazine exerts other important effects on the central nervous system. Aggressive untamed monkeys can be rendered placid and unafraid; sham rage in domestic cats is abolished; there is some evidence that at least part of its tranquillising action takes place in the posterior hypothalamus. In overactive psychiatric patients with delirium and confusional states, chlorpromazine exerts a quieting effect; aggressiveness subsides and cooperation is established; the need for electroconvulsive therapy is greatly diminished. Chlorpromazine, like reserpine, antagonises the action of lysergic acid diethylamide (p. 221).

*Toxic Effects.* In view of the multiplicity of actions of this drug it is not surprising that there is also a wide variety of side-effects.

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A slight fall in blood pressure and some increase in cardiac rate may be seen with ordinary dosage; the patient may complain of lightheadedness, dryness of the mouth, nausea and slight constipation. More serious toxic effects are referable to the liver, bone marrow, skin and central nervous system. About 2 per cent of patients who are treated with chlorpromazine develop jaundice, and this complication is most likely to occur if courses of treatment are prolonged. The jaundice is due to intracanalicular biliary stasis: it is not caused by parenchymatous liver disease. The prognosis is good if the drug is promptly withdrawn. Depression of bone marrow with resultant blood dyscrasias has been reported with fatal outcome in a few cases. Skin rashes occur in about 10 per cent of patients receiving chlorpromazine. Suicidal depression may occur. Prolonged administration of the drug, especially in high dosage, may produce the signs and symptoms of Parkinsonism—a toxic effect shared with reserpine (p. 318); these signs of Parkinsonism may persist on withdrawal of the drug. Chlorpromazine is readily absorbed after ingestion or after intramuscular injection. A single dose acts for about 6-8 hours and less than 10 per cent is recovered unchanged in the urine.

Chlorpromazine Hydrochloride is available in tablets of 10, 25 or 100 mg. The total daily dose is usually 75-150 mg. in divided doses, but in some patients the optimum total daily amount is 600-800 mg. Chlorpromazine may be given intramuscularly in a dose of 75-100 mg.; for an immediate effect, up to 200 mg. well diluted with normal saline may be injected intravenously. A large number of related phenothiazine derivatives have been introduced as tranquillisers but there is no evidence that any one is more potent and less toxic than chlorpromazine.

The second group of tranquillisers comprises those drugs which are used predominantly in the treatment of the neuroses. Nothing is known about the biochemical actions of these drugs on cells of the central nervous system.

## METHYLPENTYNOL

Methylpentynol ("Oblivon") is a higher alcohol and has a mild sedative action similar to ethyl alcohol (p. 181), being rapidly absorbed after oral administration. The initial claims that calm-

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ness and relaxation could be produced without accompanying drowsiness have not been substantiated; indeed in one trial using the double-blind technique, methylpentynol could not be distinguished from inert substances when given to children prior to dental extractions.

*Toxic Effects.* Methylpentynol can give rise to skin rashes and exfoliative dermatitis has been reported. Laboratory evidence suggests a potential hepatotoxic action. Addiction to this drug may occur, especially in alcoholic subjects and its pharmacological action is synergistic with those of the barbiturates or alcohol.

Methylpentynol is available as a capsule containing 250 mg. and also as an elixir.

### BENACTYZINE

Benactyzine ("Suavatil") is 2-diethylaminoethyl benzilate hydrochloride. It has an atropine-like action. The drug is said to act by selectively blocking nerve pathways in the hypothalamus, thus protecting the higher centres of the brain from disturbing stimuli. When tested in animals, it can produce a state of indifference to disturbing stimuli, but in several well-controlled clinical trials in man it was found to be not therapeutically superior to inert tablets. It is probable that benactyzine is at best a feeble sedative.

*Toxic Effects.* No serious toxic effects have been reported following on the use of benactyzine but minor side-effects are common. These include dizziness, lack of concentration, heaviness in the limbs, dryness of the mouth and difficulty in reading small print.

Benactyzine is available in 1 mg. tablets and the oral recommended dose is 1-4 mg.

### HYDROXYZINE

Hydroxyzine ("Atarax") is a chlorobenzhydryl derivative and has antihistaminic properties (p. 283). It acts as a depressant of the central nervous system and has been recommended in the treatment of patients with dermatoses in whom emotional tension

## DRUGS ACTING ON THE NERVOUS SYSTEM

is an important factor. Side-effects are infrequent and include headache, drowsiness, dryness of the mouth and pruritus.

Hydroxyzine is given orally as tablets in a dose of 10 mg. four times daily after meals, increased if necessary up to 25 mg. four times daily.

### MEPROBAMATE

Meprobamate ("Equanil") is 2:2-di(carbamoyloxymethyl) pentane and is still the most popular of the tranquillisers for the treatment of the neuroses. Meprobamate has an action similar to mephènesin (p. 241) in that it blocks multineuronal reflexes and thus relaxes muscular tone. It also has a mild action on the sensory cerebral cortex similar to that of the barbiturates. It has been reported that a tranquillising effect can be produced by the drug without clouding of consciousness, possibly due to relaxation of voluntary muscle tone. Controlled clinical trials indicate that meprobamate is a moderately active sedative of no greater value than sedative doses of amylobarbitone or phenobarbitone.

*Toxic Effects.* Meprobamate may cause addiction; other toxic effects include hypotension, an erythematous itching rash, diarrhoea and more seriously, purpura or convulsions.

Meprobamate is available for oral administration as a tablet of 400 mg. The usually recommended daily dose is 400-1,600 mg. for relief of anxiety and mental tension.

It will be noted that although the tranquillising drugs which are recommended in the neuroses and minor functional disturbances have been reported to relieve anxiety without impairment of initiative or alertness, there is no unequivocal evidence that any one of these is superior to well-established sedatives such as the barbiturates (p. 208).

## ✓ ANTICONVULSANT DRUGS

There are many drugs which are used in the management of patients suffering from epilepsy and similar disorders in which convulsions may occur. These preparations are classified as anticonvulsants. An alternative designation—*anti-epileptic drugs*—



is a misnomer and is being discarded. Although in practice epilepsy is the commonest cause of convulsions, there are other causes such as hypertensive encephalopathy, tetanus, and in many of the diseases of children. It must also be remembered that the term epilepsy includes transient disorders of motor power and cerebra- tion unaccompanied by convulsions.

The ideal anticonvulsant drug would have no sedative or hypnotic effect; it would be well tolerated by the patient and non-toxic to the tissues even after prolonged administration. It would have a high therapeutic index; be suitable for parenteral administration and therefore suited to the treatment of status epilepticus. For prophylaxis a long-acting drug is desirable: it can then be given infrequently—say twice or thrice daily. Before considering the drugs individually it must be emphasised that when anticonvulsant therapy is prescribed for a patient with epilepsy, the physician's objective is to suppress the fits completely. If this result can be achieved without producing side-effects from drug therapy, the patient can enjoy a normal life. No one drug can be singled out as the best anticonvulsant for all cases; indeed it is frequently found that a combination of two drugs is more effective than a single one.

### (1) BARBITURATES

All the barbiturates that are clinically active could theoretically be used in order to suppress epilepsy. Most of the barbiturates, however, are unsuitable because—in the dose necessary for this purpose—they also cause troublesome drowsiness. Phenobarbitone is the barbiturate of choice because, in therapeutic doses, it selectively depresses the motor cortex and has a relatively slight action on the higher centres. The epileptic appears to be rather more tolerant of phenobarbitone than is the normal person. Thus, moderate doses (30 mg.  $\times$  4) do not commonly inconvenience the patient, especially if the drug is given at intervals between noon and bed-time—the usual regimen in epilepsy because fits are most common during the night. When still larger doses of phenobarbitone are needed and drowsiness interferes with work or pleasure, the side-effect can be relieved or abolished by giving amphetamine sulphate (p. 142) separately (1.25–2.5 mg. before breakfast and at

midday): this small dose suffices to promote wakefulness without appreciably interfering with the anticonvulsant action.

Phenobarbitone is one of the most potent anticonvulsants known. It has a wide margin of safety and acts for 8-12 hours (see p. 220). When used in the treatment of major epilepsy ("grand mal") it is usual to prescribe 60 mg. thrice daily, increasing this if necessary to a maximum total dosage of 360 mg. daily. Should the seizures not be controlled by this dosage, it is preferable to combine phenobarbitone with another anticonvulsant such as phenytoin sodium (see below). Phenobarbitone is effective in controlling 70 per cent of patients with major epilepsy, but it is less effective in psychomotor attacks and of no value in the control of "petit mal". When the drug is found to be effective, therapy should be continued for two years after the last seizure and then it should be withdrawn gradually. An epileptic may develop a series of fits terminating in prolonged unconsciousness. This condition—called *status epilepticus*—is usually the outcome of suddenly stopping drug therapy. The condition constitutes a medical emergency. The patient should receive sodium phenobarbitone 180 mg. in solution by intramuscular injection, and this dose may be repeated within one hour if the patient is not responding favourably.

When phenobarbitone has proved more or less ineffective in suppressing major epileptic attacks, substitution of a different anticonvulsant drug is indicated. This must not be done abruptly: during the first week of treatment with the new anticonvulsant, phenobarbitone therapy is continued and from the 7th to the 10th day it is gradually withdrawn. Sometimes it is found desirable to continue treatment with *both* drugs.

## (2) PHENYTOIN SODIUM

Phenytoin Sodium (synonyms—Soluble Phenytoin; Diphenylhydantoin Sodium; "Epanutin"). This synthetic compound is a white crystalline powder which is freely soluble in water; the solution is alkaline and irritant, and phenytoin sodium should not therefore be administered subcutaneously. Although phenytoin sodium is closely related chemically to the barbiturates, being a derivative of glycolyl urea instead of malonyl urea (see p. 208),

this drug has no sedative action. The anticonvulsant effect is of great value in the treatment of major epilepsy and of psychomotor manifestations of epilepsy. Phenytoin sodium is ineffective in petit mal, status epilepticus, myoclonic seizures or other types of convulsions such as those of tetanus. The mode of action of phenytoin sodium is unknown.

*Toxic Effects.* About 15 per cent of all patients receiving phenytoin sodium show toxic effects; some of these are mild, but others are so severe as to necessitate withdrawal of the drug. Irritation of the gastric mucosa may occur because of the strong alkalinity of the solution, and this results in nausea, epigastric discomfort and vomiting. Stimulation of the central nervous system may occur with overdosage and the patient may exhibit restlessness, ataxia, slurred speech, nystagmus and headache. Skin rashes are seen in up to 10 per cent of patients, but these are usually mild and of erythematous or morbilliform nature; exfoliative dermatitis—a serious complication—has been reported during therapy. A curious and interesting side-effect, namely, hyperplasia of the gums, is seen in some patients taking phenytoin sodium. The frequency of this phenomenon is difficult to assess: it is variously reported as occurring in 5-50 per cent of all patients receiving the drug. It is more common in children and young adults, perhaps because it does not occur in edentulous mouths, and it may occur during the first few months or only after years of therapy. Histological examination shows only proliferation and hypertrophy of normal structures.

*Absorption, Fate and Excretion.* Phenytoin sodium is well absorbed from the alimentary tract and although the details of its fate are unknown, it seems likely that most of it is metabolised in the liver; only a small fraction appears unchanged in the urine, the remainder being conjugated with glycuronic acid.

Phenytoin sodium is most commonly prescribed for the treatment of major epilepsy, either in conjunction with phenobarbitone or alone after phenobarbitone has been found to be ineffective. In either case the dose schedules of the two drugs should be dovetailed over a period of 7-10 days, or the incidence of seizures

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may increase. Phenytoin sodium is available in tablets of 50 or 100 mg. and the dose is 50-100 mg.; a suitable schedule for the treatment of major epilepsy would be 100-200 mg. thrice daily.

### (3) METHOIN

Methoin ("Mesontoin"), 3-methyl-5:5-phenylethylhydantoin, is related both chemically and pharmacologically to phenytoin sodium. By contrast with phenytoin, it has an appreciable sedative effect but this falls short of the sedative action of phenobarbitone. Toxic effects are less frequent than with phenytoin sodium, but methoin may give rise to grave complications including aplastic anaemia and toxic hepatitis. The consequences of these side-effects are so serious that few physicians would use the drug except as a last resort in an intractable case of major epilepsy. The dose of methoin is 50-100 mg. thrice daily, given orally.

### (4) PRIMIDONE

Primidone ("Mysoline") is a synthetic compound which was first prepared in 1949. It is related chemically to phenobarbitone in that the oxygen of the urea is replaced by two atoms of hydrogen. It is a white crystalline powder, insoluble in water. Primidone is a relatively non-toxic drug useful in the treatment of major epilepsy and in some cases of petit mal. It is readily absorbed from the alimentary tract and is probably metabolised in the liver.

*Toxic Effects.* Although it is more toxic than phenobarbitone, the side-effects which arise during therapy with primidone are not usually serious. Nausea, vertigo, ataxia and skin rashes occur, but these tend to diminish with continuation of therapy. Primidone is available in 250 mg. tablets and the dose is 500-2,000 mg. daily in divided doses. Primidone may be used concurrently with phenobarbitone or phenytoin sodium.

### (5) TROXIDONE

Troxidone (Trimethadione) is 3:5:5-trimethyloxazolidine-2:4-dione, a substituted hydantoin. Troxidone was first synthesised in 1944 and was originally studied as an analgesic, but it was not

until 1946 that it was found to be specific in the treatment of the type of epilepsy called petit mal.

Troxidone is a white crystalline powder slightly soluble in water. Its pharmacological actions are confined to the central nervous system. Here it has a suppressive action specific to petit mal: the E.E.G.s of many patients with petit mal revert to normal under treatment with troxidone. The mode of action of the drug is unknown but it has analgesic power similar to that of codeine (p. 256). In therapeutic doses troxidone has no other significant actions, but the *toxicology* of the drug is important. Drowsiness is not uncommon during the first few days of treatment, but this usually disappears with continued administration. Blurring of vision in bright light (the "glare" phenomenon) is also common under troxidone therapy, being reported in up to 75 per cent of patients; this symptom is relieved simply by wearing dark glasses. Ocular scotomata may also develop, and repeated examination of the eyes should be carried out to detect these; should any abnormality be found the drug should be withdrawn. Less common but more dangerous toxic effects from troxidone are skin eruptions and blood dyscrasias. Morbilliform skin rashes are seen and exfoliative dermatitis may develop. In practice, the most serious danger is the possible development of agranulocytosis, thrombocytopenia or aplastic anaemia. Close supervision of troxidone therapy is therefore essential, especially during the first month -- when individual sensitiveness is likely to be noticed.

*Absorption, Fate and Excretion.* Troxidone is readily absorbed from the intestine, is almost totally metabolised, probably in the liver, and only traces of the drug appear in the urine. Troxidone is available in 300 mg. capsules or 150 mg. tablets for oral administration. In the treatment of petit mal the dose is up to 2,000 mg. daily in divided doses.

## ⑥ BROMIDES

Bromide was first recommended for the treatment of epilepsy in 1857 and prior to the discovery of the barbiturates it was the principal therapeutic agent in this disease. With the development of less toxic and more specific anticonvulsant drugs, bromide is rarely or

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never used in the treatment of epilepsy. The inorganic salts of bromine (sodium bromide, potassium bromide and ammonium bromide) in clinical use are white crystalline powders and they are freely soluble in water.

**PHARMACOLOGY.** The action of the bromide ion on the central nervous system is a depressant one; it is non-specific in its site of action. In therapeutic doses, bromide eventually produces drowsiness, diminished power of concentration, and apathy. With larger doses, speech is slurred, movement is slow, and muscular weakness may develop through depression of the motor cortex; memory is impaired. Larger doses cause severe lethargy, confusion and muttering, delirium, and finally coma. Doses above the usual therapeutic range are required to alter electro-shock convulsions in man. The mechanism of action of the bromide ion on the nerve cell is obscure but it is probable that the depressant action is a direct one and is not dependent on changes in level of chloride ion (see below).

*Absorption, Fate and Excretion.* Bromide is readily absorbed but in high concentrations it may cause gastric irritation with vomiting (action of a hypertonic salt solution). The bromide ion mixes with the chloride ion in the extracellular fluid and the total concentration of halide in this fluid is maintained at a physiological level of about 100 m.Eq./litre. The kidney, however, excretes chloride to a greater degree than bromide, so that during bromide administration there is an absolute fall in the extracellular chlorides. Bromide is only slowly eliminated from the body and after a single dose of sodium bromide, traces are found in the urine for several weeks. Repeated dosage with bromide leads to *cumulation* (see p. 17). The rate of bromide excretion can be increased by ingestion of chloride—which raises the level of total halide in the extracellular fluid; this phenomenon constitutes the basis of treatment in bromide poisoning.

*Toxic Effects.* *Acute* bromide poisoning is rare as the vomiting of gastric irritation usually prevents absorption. Chronic poisoning is known as *bromism* and the signs and symptoms are referable to the central nervous system and also to the routes of excretion of the bromide ion through the skin, glandular secretions and gastrointestinal tract. The characteristic rash usually appears as “bromide acne” which affects principally the face and shoulders but may involve other parts of the body; other skin rashes may occur. Head-

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ache, coryza and conjunctivitis may occur due to the effect on the secretory cells of the paranasal sinuses, eyes and upper respiratory passages. Anorexia, furred tongue, dyspepsia and constipation are common. The signs in the central nervous system are mostly those of exaggerated pharmacological actions, such as ataxia, muscular weakness and extensor plantar responses, but a specific bromide psychosis has been described. The treatment of bromide intoxication consists in withdrawing the drug and giving large doses of sodium chloride and water.

The dose of Sodium Bromide or Potassium Bromide is 0.3–1.2 G. In the treatment of major epilepsy a daily dose of 2 G. may be given, and this is increased by 0.3 G. daily in subsequent weeks until the seizures are checked. Bromide is neither a reliable nor a rapidly effective hypnotic, as a single dose does not produce an adequate blood level of the bromide ion. The efficacy of hypnotics such as the barbiturates (p. 208), chloral hydrate (p. 215) or paraldehyde (p. 217) has rendered "bromide" an obsolete drug.

## RELAXANTS OF VOLUNTARY MUSCLE

These drugs are also called "neuromuscular blocking agents": they act at the myoneural junction in voluntary muscles. When a physiological motor impulse arrives at the myoneural junction, acetylcholine is released at the nerve ending and depolarises the muscle endplate, causing a transient electrical charge called the *endplate potential*. This current of depolarisation excites the adjoining muscle fibre and causes contraction of muscle; the effect is transient because the released acetylcholine is rapidly hydrolysed to inactive choline and acetic acid by cholinesterase (p. 112)—which is readily available in skeletal muscle: the endplate quickly returns to its resting polarised state and it is then ready to respond to the next nerve impulse.

The drugs commonly used as voluntary muscle relaxants may be conveniently considered in three groups:

(i) The competitive neuromuscular blocking agents (or "blockers") or *non-depolarisers* (for example (+)-*d*-tubocurarine hydrochloride) compete with acetylcholine for receptor sites on the muscle endplate. Tubocurarine does not cause depolarisation

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and therefore the size of the endplate potential is reduced in proportion to the number of receptors occupied by this drug.

(ii) The *depolarisers* resemble acetylcholine so closely that they not only compete for receptor sites on the muscle endplate but also cause depolarisation—and consequently an endplate potential. The essential difference between the action of the depolarising muscle relaxants and acetylcholine lies in the *duration* of the endplate potential; normally it lasts for a few milliseconds, but with drugs of this group such as suxamethonium and decamethonium the endplate potential may persist for minutes or even hours. The endplate potential produced by the depolarising blockers spreads to the surrounding muscle membrane, rendering the muscle inexcitable. The state of neuromuscular block is abolished by any procedure which tends to repolarise the endplate.

(iii) There is a third group of voluntary muscle relaxants in which the drugs have mixed actions, initial depolarisation being followed by a non-depolarising competitive type of block.

Although this rigid classification of the voluntary muscle relaxants is of practical value in therapeutics it should be noted that a blocking agent (for example, decamethonium) may produce depolarising effects in one animal species and non-polarising effects in another species.

### TUBOCURARINE CHLORIDE

Tubocurarine Chloride, a white, odourless, crystalline powder, is the chloride of an alkaloid (+)-tubocurarine obtained from the stems of plants of the genus *chondrodendron*. It is a quaternary ammonium compound—a chemical structure common to all muscular relaxants which are at present used therapeutically. The isomer (—)-tubocurarine is much weaker than the (+)-tubocurarine.

On injection intravenously tubocurarine causes paralysis of voluntary muscles without initial stimulation, by producing a non-depolarising block at the muscle endplate. Not all voluntary muscles are equally affected: within 60–90 seconds after injection



tion into a conscious subject he develops ptosis, followed by weakness of the muscles of the face and jaw, and there is a sensation of tightness in the throat with difficulty in speaking and swallowing. Weakness of the neck muscles follows and then paresis of the muscles of the abdomen and limbs. The respiratory muscles are the last to be affected and this results in shallow breathing or even cessation of breathing—if the dose is large enough. Recovery of muscle takes place in the reverse order. If an appropriate dose of tubocurarine is given during surgical operation to produce the desired *abdominal relaxation*, the intercostal muscles will almost certainly be paralysed, and the anaesthetist must be prepared to use assisted or controlled respiration. Tubocurarine blocks transmission through autonomic ganglia by competition with acetylcholine at preganglionic nerve endings. In therapeutic doses tubocurarine has no effect on the central nervous system: sedative and analgesic actions are entirely absent, and therefore other drugs must be used at surgical operation to ensure unconsciousness and to abolish appreciation of pain. Tubocurarine releases histamine from the tissue cells and on rare occasions this results in bronchospasm. On the cardiovascular system tubocurarine produces little change, but there may be a slight rise in blood pressure; occasionally a fall in blood pressure occurs, possibly following histamine release or as a result of blocking of transmission at sympathetic ganglia. Tubocurarine does not appear to protect the heart against vagal inhibition during anaesthesia. Salivary and bronchial secretions are occasionally increased and very large doses of the drug may produce loss of tone of smooth muscle in the gastro-intestinal tract and urinary bladder.

*Absorption, Fate and Excretion.* Tubocurarine is not absorbed through the intact skin, and it is inactive orally unless given in very high dosage. After intravenous injection it is widely distributed in body tissues, and this in itself is an important factor in explaining the brief duration of its action. A single dose given intravenously acts in 60-90 seconds and the drug remains effective for 30-40 minutes. In man, about one-third of the injected dose is excreted unchanged in the urine within a few hours, the remainder being destroyed in the body, possibly in the

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liver and the kidney. No significant amount crosses the placenta and therefore (+)-*d*-tubocurarine may be used in obstetric practice.

*Toxic Effects.* Excessive doses merely cause exaggerated pharmacological actions, and it is therefore easy to forecast the dangers to which the patient is exposed. The most important effect is paralysis of the respiratory muscles. Regurgitation of gastric juice into the œsophagus is also liable to occur. This is attributable to the flaccid state of the diaphragm and to the effect of a *large* dose of tubocurarine in paralysing the sphincter at the lower end of the œsophagus. The accumulation of gastric juice in the œsophagus is potentially dangerous: it may cause local ulceration; and also when artificial respiration is instituted by the anæsthetist the fluid in the œsophagus may be sucked into the trachea. Tubocurarine and similar drugs should not be used in patients suffering from myasthenia gravis (p. 117). Anæsthetic ether has curarising properties and the dose of tubocurarine required with it is about one-half of that usually recommended.

**ANTIDOTES.** The pharmacological antidotes to non-depolarising relaxants are the anticholinesterases (p. 115); neostigmine is the drug generally used. Their action is mainly that of inhibiting cholinesterase, thus allowing a larger amount of acetylcholine to accumulate at the endplate; but the cholinesterases appear to have also a direct action on motor endplates, increasing their sensitiveness to acetylcholine. If neostigmine methylsulphate is used it should be given intravenously in a dose of 5 mg. and "assisted respiration" continued for as long as may be necessary. Because of the undesirable parasympathomimetic side-effects of neostigmine, this injection should be preceded by intravenous injection of 1·2 mg. of atropine sulphate. It should be noted that atropine blocks the cholinergic effects of neostigmine on the viscera, but it does not interfere with the transmission of impulses at the motor endplates.

*Preparation and Dosage.* Tubocurarine Chloride Injection is given intravenously in a dose determined by the physician accord-

ing to the needs of the patient. It contains 1 per cent w/v of tubocurarine chloride. A suitable schedule is to give 10 mg. initially and if relaxation is insufficient in 3 minutes, a supplementary dose of 5 mg. is given. No curare-like drug should be given within 30 minutes of the completion of the operation, as the effects of muscular relaxants are very distressing to the conscious patient. Many proprietary preparations containing tubocurarine chloride are available. Their strengths vary greatly and extreme care must be observed when assessing the appropriate dosage.

*Uses.* Tubocurarine chloride is used chiefly as an adjuvant to anaesthesia in order to obtain greater muscular relaxation during surgical operations and to facilitate orthopaedic manipulations. Safe administration of this and similar drugs requires the skill of an expert anaesthetist and the technical details are fully described in textbooks of anaesthesia.

#### DIMETHYL TUBOCURARINE

The dimethyl ether of *d*-tubocurarine iodide is about three times more potent than *d*-tubocurarine chloride, and it is reported that side-effects due to liberation of histamine are less frequent after using this relaxant. The average initial dose is 2–4 mg.; and its pharmacological actions are similar to those of *d*-tubocurarine. It is also available as the bromide or chloride.

#### GALLAMINE TRIETHIODIDE

Gallamine Triethiodide ("Flaxedil") is a white amorphous powder first synthesised in 1915. It has a curare-like action but has about one-fifth the potency of tubocurarine: 80 mg. of gallamine is equivalent to about 15 mg. of tubocurarine chloride. The drug has also less effect than tubocurarine in blocking transmission at sympathetic ganglia and in releasing histamine, but gallamine tends to cause tachycardia by an atropine-like vagal antagonism. In the presence of carbon dioxide accumulation during anaesthesia, gallamine may cause ventricular tachycardia. The duration of action of gallamine is about half that of tubocurarine, and it is therefore useful for operations lasting 20–30

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minutes. The actions of gallamine in man are not enhanced by ether. It crosses the placental barrier and should therefore not be used in obstetric practice; the use of gallamine is of course contraindicated in patients suffering from myasthenia gravis.

*Preparations and Dosage.* Gallamine Triethiodide Injection is dispensed in a sterile solution of sodium sulphite (0.2 per cent). The official preparation is labelled to show the strength of the solution and the amount of gallamine triethiodide in a suitable dose-volume. The solution should be protected from light. "Flaxedil" is available as a 4 per cent solution of gallamine triethiodide in ampoules of 2 and 3 ml. and in multi-dose containers of 10 ml. The approximate dose in man is 1 mg. per Kg. intravenously: the effect of this dose persists for 15-30 minutes. A dose of 2 mg. per Kg. usually produces apnoea. Gallamine is antagonised by neostigmine.

### DECAMETHONIUM IODIDE

Decamethonium ("C10") is bistrimethylammonium decane and although it is a member of the methonium series (p. 153) its outstanding pharmacological action is as a voluntary muscle relaxant. It produces a *persistent* depolarisation of the motor endplate similar to that caused by high concentrations of acetylcholine; the endplate potential is reduced below that required to propagate an electrical response in a muscle fibre; it also renders the adjacent muscle inexcitable. It is important to remember that neostigmine which antagonises tubocurarine and gallamine triethiodide is ineffective against decamethonium and indeed may enhance the C10 effect. Prior to producing paralysis, decamethonium may cause temporary muscular fasciculation—seen especially over the chest and abdomen; this is associated with the phase of depolarisation of the motor endplate.

Decamethonium does not produce significant ganglionic block; and release of histamine occurs only after large doses. Its anticholinesterase effect is weak and does not contribute in any important way to its actions. Because of these differences from tubocurarine, bronchospasm and hypotension are not commonly seen clinically with decamethonium.

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*Toxic Effects.* The important untoward effects are accounted for in terms of an exaggerated pharmacological action: respiratory paralysis occurs when there is full muscular relaxation.

In patients who are sensitive to iodides, there is a risk of *iodism* when decamethonium iodide is given.

*Absorption, Fate and Excretion.* After intravenous injection, decamethonium is widely distributed in the extracellular fluid and is not metabolised in the body; about 60 per cent is recovered unchanged in the urine within 3 hours and 80-90 per cent within 24 hours. Excretion is delayed in renal failure. The muscular relaxant effect is seen within 60 seconds and the action lasts from 10 to 20 minutes. Decamethonium does not cross the placental barrier: it may therefore be used to ensure muscular relaxation in labour and during Caesarian section.

*Dosage.* Decamethonium is five times more potent than tubocurarine in man, and the recommended dose is about 40  $\mu$ g. per Kg. intravenously. In brief, the procedure is to give an initial dose of 2-3 mg. at a rate of 1 mg. per minute; after 10-30 minutes a further dose of 1-3 mg. is given.

*Preparations.* Decamethonium dibromide is also known as "Syncurine", the di-iodide as "Eulissin"; each is supplied in solution containing 2 mg. per ml.

### SUXAMETHONIUM CHLORIDE

Suxamethonium chloride (Succinylcholine chloride, "Scoline") is the most generally used short-acting relaxant. It causes depolarisation of the voluntary muscle endplate and it can be regarded as a short-acting decamethonium (p. 237). The initial stimulation of muscular fasciculation is even greater than with decamethonium. There is, as with decamethonium, antagonism between suxamethonium and the competitive blocking drugs, tubocurarine and gallamine. In single small doses suxamethonium does not act on autonomic ganglia or viscera, although occasionally vagal inhibition of the heart has been reported. Large doses may cause a muscarine-like action with resultant hypotension

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but this is readily prevented by giving a preliminary injection of atropine.

*Absorption, Fate and Excretion.* Within 12-15 seconds of intravenous injection diffuse uncoordinated muscular contractions are seen which persist for about 15 seconds; full paralysis then develops, lasts for 2-6 minutes and muscle power returns to normal in a further 3-4 minutes. This brief action of suxamethonium is attributed to the fact that it is hydrolysed rapidly by pseudocholinesterase in the plasma to succinylmonocholine and choline and thereafter more slowly to succinic acid and choline by both pseudocholinesterase and true cholinesterase. Only about 2 per cent of the injected dose of suxamethonium is excreted in the urine.

In a few patients the action of suxamethonium is prolonged over the usual 3-4 minutes; the explanation may be that these patients have an abnormally low plasma level of pseudocholinesterase. The majority of such reports have referred to ill patients suffering from severe anaemia, liver disease, thyrotoxicosis or electrolyte imbalance. Other causes of prolonged apnoea include overdosage of the relaxant, reflex laryngeal spasm and abnormal amounts of carbon dioxide in the blood stream; hypothermia may also prolong the action of suxamethonium.

*Dosage.* The dose of suxamethonium varies with the particular requirements: 0.1-0.2 mg. per Kg. produces satisfactory relaxation of peripheral muscles for up to 3 minutes with very little effect on respiration; 0.3-0.4 mg. per Kg. depresses respiration, and the relaxant effect lasts for up to 5 minutes; 0.5-1 mg. per Kg. produces complete relaxation for 5-10 minutes and necessitates artificial respiration.

Intravenous injection of 0.1 per cent solution of suxamethonium has been recommended in order to prolong its relaxant effect, but a few patients exhibit prolonged apnoea after cessation of the drip; this may be due to an accumulation of succinylmonocholine, itself a weak depolarising muscle relaxant.

*Therapeutic Uses.* Suxamethonium is a particularly suitable drug for use when rapid brief muscular relaxation is required. Thus it is

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often used during endoscopy, for the control of electro-convulsion therapy, and to facilitate orthopædic manipulations.

ANTIDOTES to the competitive non-depolarising muscle relaxants mostly belong to the anticholinesterases, and those which are most commonly used are Neostigmine Methylsulphate and edrophonium chloride ("Tensilon"). Neostigmine methylsulphate (prostigmine) has already been described (p. 235) with regard to its anticholinergic effect, and it remains to emphasise that it should never be injected intravenously for this purpose without first giving atropine sulphate by the same route, in order to prevent cardiac arrest from the sudden inhibiting effect of a cholinergic drug acting through the vagus.

### EDROPHONIUM ("Tensilon")

Edrophonium chloride resembles neostigmine in its actions, but its effect on skeletal muscle is more conspicuous than its effect on autonomic ganglia or cholinergic visceral receptors. Atropine sulphate should always be given intravenously before edrophonium is administered; otherwise parasympathomimetic effects may occur—such as sweating, salivation, diarrhoea and bradycardia. The principal difference in practice from neostigmine is in the rapidity of action of edrophonium. After intravenous injection, the anticholinergic effect of edrophonium is seen within one minute and it lasts for only 2–3 minutes. The action of edrophonium in man is less certain than that of neostigmine.

True antidotes to depolarising blockers are known; for example, pentamethonium and hexamethonium both reverse the action of decamethonium but their use is impracticable because they may produce undesirable side-effects: there is a considerable risk of inducing arterial hypotension if hexamethonium is used in this way.

## DRUGS USED IN PARKINSONISM

In addition to the drugs which are classified as true anticonvulsants, there are others which have a selective depressant action on the central nervous system and combat excessive motor activ-

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ity; these may be classified as *centrally acting muscle relaxants* and include mephenesin and the synthetic drugs used in the treatment of extrapyramidal rigidity.

### MEPHENESIN

Mephenesin ("Myanesin")  $\beta$ -dihydroxy- $\gamma$ -(2-methylphenoxy)-propane is a synthetic aromatic glycerol ether. It interferes with conduction in multineuronal reflexes in the spinal cord and probably also in central subcortical polysynaptic reflexes; the monosynaptic reflex is not affected by mephenesin. As a result of this action, relaxation of voluntary muscles occurs, without clouding of consciousness. Mephenesin is also a local anaesthetic: it is as powerful as procaine (p. 169), but it is too irritant locally on injection to be useful in practice for this purpose.

*Toxic Effects.* On oral administration, anorexia, nausea and vomiting may occur. Nystagmus, diplopia, lassitude and muscle incoordination have been reported and intravenous injection of excessive amounts of mephenesin may result in local phlebotrombosis, intravascular hæmolysis and anuria.

*Absorption, Fate and Excretion.* Mephenesin is rapidly absorbed after oral administration. It is widely distributed in the body, being concentrated slightly in nervous tissue. It is probably metabolised in the liver: breakdown is rapid; only traces of the drug are detectable in the plasma 1 hour after intravenous injection.

Mephenesin may be given orally as an elixir containing 100 mg. in 1 ml.; the oral dose is 0.5–1 G. It may be administered slowly intravenously in a dose of 0.5–3 G. as a 10 per cent solution of mephenesin. This drug is on occasion of temporary benefit in conditions of voluntary muscle spasm such as tetanus, disseminated sclerosis or Parkinsonism: its effect is much more reliable on intravenous than on oral administration.

Although drugs of the atropine series (p. 126) and some of the antihistamines (p. 285) are known to be useful in the treatment of extrapyramidal disease such as Parkinsonism, newer synthetic drugs are available for this condition.



## BENZHEXOL HYDROCHLORIDE

Benzhexol Hydrochloride ("Artane") is a white crystalline water-soluble powder. Its peripheral effects are similar to, but much weaker than, those of atropine. In animals it reduces tremors induced by central stimulation with nicotine, but in excessive doses benzhexol causes cerebral stimulation. When given in the treatment of Parkinsonism the relief of rigidity is more marked than the effect on tremor; this contrast is seen with all drugs used in this disease. The mechanism by which benzhexol provides relief of spasm and tremor is unknown.

Benzhexol is rapidly absorbed after oral administration and its fate within the body is unknown. Nausea and epigastric discomfort may occur and the initial doses of the drug should be small (1-2 mg.) and taken with meals. Headache, mydriasis, dry mouth and restlessness may be seen early in therapy, but the side-effects usually subside with continued dosage.

Benzhexol is available as 2 mg. and 5 mg. tablets and the initial dose of 1-2 mg. daily may be gradually increased to 20 mg. daily, in accordance with the needs of the patient.

## DIETHAZINE HYDROCHLORIDE

Diethazine Hydrochloride ("Diparcol"), a white, crystalline, water-soluble powder, is diethylaminoethyl-N-dibenzoparathiazine; it is chemically related to the phenothiazine group of antihistamine drugs (p. 282). Diethazine was introduced as therapy for Parkinsonism because of the known benefits derived from certain members of the antihistamine group. The effects of diethazine on the central nervous system are poorly understood. It has no significant antihistaminic action, but has moderate parasympatholytic and weak adrenolytic effects. When taken orally it is rapidly absorbed but its subsequent fate in the body is unknown. The toxic effects of diethazine may be severe. In addition to dyspepsia, vertigo, increase in tremor and muscle weakness, cases of agranulocytosis and renal damage have been reported. In view of the variable reports as regards the efficacy of this drug in the treatment of Parkinsonism, and the dangers of toxic side-effects,

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other drugs are to be preferred for the treatment of spastic disorders.

Diethazine is given orally, the initial dose being small. The total daily dose is 1-3 G. given with meals.

### CARAMIPHEN HYDROCHLORIDE

Caramiphen Hydrochloride ("Parpanit") has peripheral actions like those of atropine, but is much weaker than the latter. It also possesses some adrenolytic and antihistaminic actions. The mode of action in the central nervous system in patients with Parkinsonism is not understood. Caramiphen is readily absorbed after oral administration and it is then probably metabolised in the liver and kidney. Side-effects occur in about 60 per cent of those receiving caramiphen; the most common are giddiness, nausea and epigastric discomfort. The drug is given orally with meals and the initial dose should not exceed 12.5 mg. five times daily. This dose is gradually increased to the limit of tolerance for the individual patient; total daily doses of 200-600 mg. have been given.

### "DISIPAL"

"Disipal" 2-(phenyl-*o*-tolylmethoxy)ethyl dimethylamine hydrochloride is a synthetic spasmolytic used in the symptomatic treatment of Parkinsonism; the relief of rigidity is more marked than that of tremor. It reduces the dribbling of saliva of this disease. The side-effects of disipal are parasympatholytic, similar to those of benzhexol hydrochloride. Disipal is given orally in doses of 50 mg. thrice daily, increasing the dose gradually to the limit of individual tolerance.

### ETHOPROPAZINE HYDROCHLORIDE

Ethopropazine Hydrochloride ("Lysivane") is 10-(2-diethylaminopropyl)phenothiazine hydrochloride. The major actions are parasympatholytic and spasmolytic, but in therapeutic use its main effect is to relieve hypertonus. Muscular rigidity is usually reduced and the tremor may become less severe, but dribbling of saliva usually persists. An improvement may thus be obtained in muscular activity, gait, facies and posture. The initial total daily

dose should be 50-200 mg. in divided doses taken with meals. The dose is then gradually increased over two to three weeks to the limit of tolerance, which is usually 150-500 mg. daily. If treatment is being withdrawn, this should be done gradually or an exacerbation of symptoms may result. The common side-effects are lethargy, drowsiness and vertigo—most frequently encountered in the early stages of therapy. Gastro-intestinal upsets are also found and muscular cramps, paræsthesiæ and confusion occur occasionally.

## CHAPTER 8

# ANALGESICS

### OPIUM

Raw opium is the juice which is obtained by incising the unripe seed capsule of the poppy, *Papaver somniferum*. It is allowed to dry by spontaneous evaporation and can then be used to make the pharmacopœial preparation Powdered Opium—which is standardised to contain 10 per cent of morphine.

Opium contains a large number of alkaloids, but only a few are clinically important, and they fall into two distinct groups: 1. Phenanthrene alkaloids, named morphine, codeine and thebaine; 2. *Isoquinoline* alkaloids, the most important of which are papaverine and narceine. After causing mild and fleeting stimulation of the higher centres, the phenanthrene alkaloids depress the central nervous system; they also *increase* the tone of smooth muscle, notably in the alimentary tract. The *isoquinoline* alkaloids have no appreciable action on the central nervous system and may produce *relaxation* of smooth muscle. The pharmacological activity of opium is predominantly due to morphine, the most important of the phenanthrene alkaloids. The pharmacological effects of morphine will therefore be described first, and thereafter some of the other alkaloids will be discussed.

### MORPHINE

**ACTION AS AN ANALGESIC.** Morphine is well described as the sovereign remedy for the relief of pain. The justification for this description lies in the *selectiveness* of the analgesic action: side-effects do occur but they are relatively insignificant, and it should be noted in particular that with appropriate doses relief of pain is achieved without interference with consciousness. It acts centrally—probably in the cortex of the frontal lobes and in the diencephalon. The mode of action is not fully understood, but it is known that morphine does not selectively depress reception

of other types of sensation such as touch, vibration, smell or hearing. It relieves both visceral and somatic pain, and is more effective in the alleviation of dull continuous pain than of sharp stabbing pain. It raises the threshold for pain perception and also alters the mental response to pain; thus the severe crushing pain of myocardial infarction may not be completely alleviated by an injection of morphine, but the patient's attitude is different: he admits the persistence of pain, but he now regards it with a degree of detachment and he regains some measure of tranquillity. If sleep be induced by morphine, the pain threshold is raised even further.

**ACTION ON THE SENSORY CORTEX AND INTELLECTUAL FUNCTION.** In small doses (10 mg.) morphine relieves pain without impairing consciousness. At the same time morphine produces fleeting stimulation of the highest centres of the brain. This accounts for the state of deep contentment, absence of disturbing emotions, and a state of mild exhilaration called *euphoria*. It is most likely to occur when the dose of morphine is rather smaller than the ordinary analgesic dose; it is readily experienced by Oriental races but in Europeans it is short-lived or entirely absent. Notwithstanding the remarkably selective action of an analgesic dose of morphine it may produce some perversion of thought: ideas may lack logical sequence, the imagination may become extravagant and—as in dream states—judgment may be impaired to the point of extinction. It is true that these phenomena are properly classed as side-effects—in relation to analgesia when narrowly considered: but the medical practitioner soon recognises that such side-effects are not infrequently a real advantage to many patients. With larger doses there are signs of depression of central sensory perception. The patient becomes drowsy and apathetic and movements are slower. At this stage, however, he can be roused by sharp sensory stimuli (pin-pricks or pinching): he can answer questions; he can stand and walk. Nevertheless if undisturbed, he soon falls asleep: the pupils are very small and breathing is slow and deep.

After a larger dose of morphine (30 mg.) the euphoric phase is not noticed: the patient passes through the analgesic stage to deep

## ANALGESICS

sleep within 15 minutes. Toxic doses produce coma in which the pupils are "pin-point" in size, the skin is cold, moist and cyanosed, and breathing is even slower (4-6 respirations per minute); and when breathing becomes *shallow* as well as very infrequent, death from respiratory paralysis is imminent. It is interesting to note that if a patient be roused from the coma of morphine overdose, he can still control muscular movements, although they are slow—showing that function in the motor area of the cerebral cortex is little affected. A corollary to this is that morphine has very little anticonvulsant effect on the cerebral motor cortex; indeed it even enhances the effect of certain central convulsants such as picrotoxin and strychnine, and therefore these should not be used in the treatment of morphine poisoning.

It is obvious that from the clinician's viewpoint the essential actions of morphine on the brain are explained in terms of depression of function. Nevertheless morphine does in fact arouse the vomiting mechanism and nausea and vomiting are therefore troublesome after-effects—especially in women. Again, in patients whose response is atypical, the euphoric phase may give place to excitement and even mania. Untoward reactions of this kind are also seen (though rarely) as a manifestation of idiosyncrasy—a circumstance which would prohibit the further use of drugs of the morphine group. It is also noteworthy that these symptoms and signs—which are extraordinary in the human subject—represent the normal response to morphine in many species of domestic animals including dogs, cats and horses.

**ACTION ON THE MEDULLA.** In man morphine has a selective depressant effect on the medullary respiratory centre and the nearby cough centre. This can be detected even with small doses which do not impair consciousness; and indeed the action is of considerable therapeutic importance in practice. The depressant action is seen also following the use of other hypnotics such as the barbiturates, but it appears only when large doses have been given (or in other adverse circumstances). Hence in practice, this effect of hypnotics (as distinct from morphine) is not deliberately sought. In therapeutic doses, morphine first diminishes the rate of respiration but there is a compensatory increase in the amplitude

of respiratory movements. The responsiveness of the respiratory centre to carbon dioxide is diminished: this leads to (a) progressive anoxæmia and (b) increasing retention of carbon dioxide in the blood and the alveolar air. In this situation it is *the state of anoxæmia itself* which provides the main stimulus to the respiratory centre. If, now, the patient inhales large quantities of oxygen the anoxæmia is abolished and respiration ceases (apnœa). It is clear therefore that the volume of oxygen inhaled should be adjusted: limitation of the amount does not deprive the patient's tissues of a desirable supplement, but the moderate restriction has two effects on the respiratory centre: (a) it continues to function under the influence of moderate oxygen deprivation; (b) partial relief of anoxæmia of the centre itself leads to recovery of the sensitiveness of these cells to the action of the natural stimulus --carbon dioxide.

Morphine and other respiratory depressants are thus seen to produce effects which closely resemble the results of certain diseases of the lungs and of the heart which also cause oxygen deprivation and carbon dioxide retention. It should be noted also that the state of depression of the respiratory centre may vary in the course of toxæmia --whatever the cause. Irregular or periodic breathing is therefore often seen. For example apnœa naturally leads to a rising concentration of carbon dioxide in the tissues and a point is reached at which the respiratory centre begins to respond: the classic Cheyne-Stokes breathing takes place; the tissues benefit by the increased oxygen intake; vigorous expiration eliminates much of the accumulated carbon dioxide---a situation which leads automatically to the next phase of apnœa. Among the therapeutic measures which are called for in such conditions is the deliberate control of the patient's oxygen supply, and the treatment ranges from artificial respiration to the use of the anæsthetists's standard equipment.

Morphine makes the medullary cough centre less sensitive to afferent vagal impulses. Thus the cough reflex is readily depressed and with large doses it may be abolished.

Nausea and vomiting occasionally follow the administration of morphine, irrespective of the route of administration. This is due to stimulation of the emetic chemoreceptor trigger zone in the

## ANALGESICS

medulla, and not to a direct action on the medullary vomiting centre, as was formerly supposed. The occurrence of vomiting after morphine appears to be a phenomenon peculiar to the individual: some always vomit; others are never affected in this way; it is common in women and relatively uncommon among men. Posture is an important factor: standing, or even sitting up make vomiting more likely, whereas the recumbent patient seldom vomits. This suggests that vestibular function is affected. Morphine has also an anti-emetic effect in that it depresses the central vomiting mechanism after preliminary stimulation. In morphine poisoning centrally-acting emetics are useless because the medullary centres are depressed.

The pupils are constricted by morphine and the "pin-point" pupils of morphine poisoning are characteristic. The mechanism of this action is uncertain. It is not produced by local instillation of morphine to the eyes. Direct stimulation of the oculomotor centre may be the mode of action; but decortication in dogs prevents the pupillary effect of morphine and this suggests that supranuclear tracts may be involved.

Vagal and vasomotor medullary centres are not depressed by morphine, unless toxic doses are given.

**ACTION ON PERIPHERAL NERVES.** Peripheral nerves are not affected by therapeutic doses of morphine. Topical applications of preparations of opium or morphine to painful areas for their supposed anæsthetic action is irrational: the alkaloid is not absorbed through the epidermis, and even if it were absorbed it would be removed by the tissue fluids, the lymphatics and small blood vessels.

**ACTION ON GASTRO-INTESTINAL TRACT.** Opium preparations are commonly prescribed for their effects on the gastro-intestinal tract. These actions also occur, however, as undesirable side-effects when morphine is given as an analgesic or narcotic. In brief, the results of opium administration in man are reduction in bowel motility and gastro-intestinal secretions, and an increase of the muscle tone. These are due principally to the direct action of morphine on the bowel and not to its effects on the central nervous



system. There is a lessening of salivary secretion and thirst is a common complaint after morphine therapy. Stomach secretions are slightly diminished, peristalsis is less frequent, but the tone of the pyloric sphincter increases. These result in considerable delay in emptying of the stomach. The secretions of the small and large intestines are reduced, and the propulsive effect of the muscle lessens, partly because of diminished peristalsis and also because there is an increase in basic muscle tone. In consequence, there is stasis of bowel contents with increased absorption of fluid, and this results in constipation. The delay in passage of the intestinal contents is increased by contraction of the muscles controlling the ilcocæcal valve. The normal sensory stimulus to defæcation may not be perceived owing to the central depressant action of morphine, and this further predisposes to constipation. Atropine partially antagonises the spasmogenic action of morphine on the colon.

Therapeutic doses of morphine cause an increase of pressure in the biliary tract by producing spasm of the sphincter of Oddi. Codeine, pethidine and amidone have a similar action. The relief gained by morphine in the treatment of biliary colic is central in type. The morphine-induced spasm of the sphincter of Oddi is relieved by nalorphine (see p. 258): it is diminished by atropine, and this is usually prescribed with morphine in the treatment of biliary colic.

**ACTION ON THE CARDIOVASCULAR SYSTEM.** Therapeutic doses of morphine have no significant effect on the action of the heart, or on the blood pressure. Following on toxic doses which depress the respiratory centre, the resultant anoxæmia depresses the vasomotor centre in the medulla causing a fall in blood pressure. Morphine causes dilatation of peripheral vessels, especially capillaries, by a direct action, possibly mediated by the release of histamine. The result is an increase in the peripheral and intracranial blood-flow—a matter of some importance in the management of patients who have concussion from head injuries.

**ACTION ON THE SKIN.** Therapeutic doses of morphine cause dilatation of the superficial blood vessels: a diffuse flush develops

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in about half an hour and it is particularly obvious on the neck and face. Congestion of the skin accounts for sweating. However, when atropine and morphine are given together (premedication by anaesthetists) though the erythema is even more obvious because of the vasodilator effect of atropine, the skin is dry—showing that the blocking action of this anticholinergic drug virtually paralyzes the sweat glands. As a sequel to the use of morphine, itching occurs occasionally and it is probably a consequence of local congestion. The skin may also be the site of idiosyncratic reactions to morphine.

**ACTION ON SMOOTH MUSCLE.** The effect of morphine on the muscles of the alimentary tract has already been described. The effects of morphine on the ureter are somewhat similar: muscle tonus increases and peristalsis is hindered. At a focus of irritability such as the site of a calculus in transit to the bladder, morphine may intensify the natural tendency for spasm to occur. This spasm can be abolished or diminished by giving full doses of atropine. The justification for administering both drugs to patients with painful ureteric colic is that the powerful analgesic action of morphine is indispensable and such aggravation of spasm as it may produce in the ureter can be relieved by the spasmolytic effect of atropine. It is interesting to note that atropine is much less effective in relieving morphine-induced spasm in the biliary tract.

**BRONCHIAL MUSCLE.** The tone of bronchi and bronchioles is increased by morphine. Hence in patients with bronchospasm, e.g. in an attack of acute bronchial asthma, it is dangerous to administer morphine.

**UTERUS.** The normal human uterus at full term is not affected by therapeutic doses of morphine.

*Action on Metabolism.* Morphine decreases slightly the metabolic rate, partly through lessening of muscle activity and partly by depressing respiration. Body temperature may be slightly lowered, again due to reduced activity and also to the peripheral vasodilatation allowing increased loss of heat. It causes a reduced

output of urine, mainly by increasing the release of antidiuretic hormone from the neurohypophysis.

*Absorption and Excretion.* The opium alkaloids are readily absorbed from the alimentary tract. After subcutaneous injection the effects of morphine are apparent in 10-20 minutes, reach a maximum in 60-90 minutes and diminish after 2-2½ hours. There are circumstances affecting absorption which are potentially dangerous. The onset of the pharmacological action depends on the normal vascularity of the tissues into which the drug is injected. Morphine is often given to patients who are in a state of surgical shock characterised by ischæmia of the superficial tissues—the result of vasoconstriction. The rate of absorption of the drug may therefore be greatly retarded and further substantial doses may be injected subcutaneously. Thus when the normal blood flow is re-established in the superficial tissues a large quantity of morphine is absorbed into the circulation. So long as the patient is under competent medical supervision it is unlikely that serious harm will come from overdose of this kind, but it is imperative that the doctor should clearly understand what is taking place so that he can intervene if the need arises.

These observations illustrate a general principle bearing on delayed absorption of drugs and they apply to any drug injected subcutaneously. There is no suggestion that morphine is dangerous in cases of surgical shock; on the contrary, in such cases morphine may be of great therapeutic value.

Morphine is largely conjugated (bound) with an unidentified substance in the liver, and to a lesser extent in the kidney. It circulates in the plasma, both in the bound and free forms, and transverse the placenta readily. About 90 per cent of an injected dose is excreted in the urine, both in bound and free forms. In man, small amounts are excreted in the lungs, sweat and faeces; only a minute quantity is found in gastric juice. Excretion of the drug begins rapidly and approximately 75 per cent of the dose can be found in the urine within 24 hours.

**TOLERANCE** to morphine readily develops on repeated administration of the drug. The exact mechanism is unknown, but it

is probable that certain cells acquire the ability to function normally in spite of what would ordinarily be excessive amounts of morphine. Tolerance does not develop to the stimulating actions of morphine on the central nervous system, nor to its effects on the eye or the bowel. Thus the morphine addict continues to exhibit small pupils and suffer from constipation.

Knowledge of variations in response to the administration of morphine is of great importance clinically. *Idiosyncrasy* in the form of nausea, vomiting, tremor and delirium has already been mentioned; there are also the *allergic* skin rashes such as urticaria and contact dermatitis. Elderly or debilitated patients require only small doses of morphine. Caution is obviously necessary in the presence of liver disease severe enough to interfere with the disposal of the drug. Similarly, in myxœdema, where metabolism is greatly reduced, patients tolerate morphine badly, and the dose of the drug should be drastically reduced in such cases.

ADDICTION. Morphine is one of the classic drugs of addiction (p. 21). This characteristic is directly attributable to its capacity to produce euphoria—an effect which appears to contribute to the total analgesic action. There is an extensive literature on the subject and the predicament of the addict is well described by De Quincey in the *Autobiography and Confessions of an Opium Eater*. When addiction becomes established there are many distressing problems for the patient and his family, and added responsibilities for the doctor. The possibility of creating a state of addiction must therefore be kept in mind. This awareness of risk constitutes the chief preventive measure. Predisposition to addiction is partly an individual characteristic; but it appears also to be racial and in the United Kingdom these factors and the vigilance of the police (who keep a close eye on drug peddlers) combine to minimise the problem as it confronts the medical practitioner. Hence although the obligations that devolve on the doctor are important, they must not be allowed to obscure the fact that when the clinical circumstances warrant it morphine should be used in appropriate doses: for example, in the management of patients in severe pain from serious injury, coronary thrombosis, acute pleurisy, acute peritonitis, and many other

conditions, the doctor prescribes morphine during the first few days without reservations about addiction. The acute phase of disease over, the risk of addiction causes the doctor to taper the dose of morphine and to turn to other measures calculated to relieve pain and distress, if such treatment is still necessary. In brief, addiction must not be made a bogey: the supreme importance of morphine should be exploited to the full for the relief of pain and distress in circumstances which are detailed in textbooks of medicine and therapeutics. Good judgment in the therapeutic use of morphine is acquired only by clinical experience and by assuming responsibility for the care of patients. One danger to be guarded against is the practice of resorting too readily to morphine to provide an easy way out of difficulties which are merely irksome to all concerned. Here the use of drugs is ethical only as a subsidiary form of treatment; and the choice of morphine would usually be imprudent. In general chronic maladies characterised by acute or subacute relapses provide a contra-indication to morphine: such are peptic ulcer, arthritis, asthma, gout and many others.

In the state of euphoria generated by morphine the patient feels the joys of escaping from reality: domestic and business worries are forgotten. This in itself may not be a serious matter, and indeed the milder states of addiction are compatible with good physical health and productive work. In the majority of cases, however, the dose required to produce euphoria must be increased as *tolerance* develops. Supplies of the drug are obtained only with difficulty and at great expense, but the compulsive urge of the addict to obtain morphine causes him to forfeit food, social position and self-respect in order to satisfy his craving. It is at this stage, and because of such self-imposed standards of living, that ill-health, emaciation and moral degradation result. The morphine addict perpetuates his habit partly because of the temporary euphoria but principally because of his fear of the withdrawal symptoms—described as the *abstinence syndrome*. The only convincing method of diagnosing morphine addiction is to observe the characteristic withdrawal syndrome which occurs when the drug is withheld or when nalorphine (p. 258) is given. The patient expresses his craving for the drug, is excitable and

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irritable and complains of nausea. Within a few hours he passes into a deep sleep, named a "yên", from which he awakens after some hours more irritable and perhaps delirious. At this stage there appear somatic signs such as diarrhoea, tachycardia, persistent yawning or sneezing, lachrymation and vomiting; the blood pressure may be elevated and pains in the limbs and abdomen are characteristic. Refusal to eat may lead to dehydration and acidosis. Should circulatory collapse occur, morphine should be given as a life-saving measure. The treatment of morphine addiction is complex, but briefly it consists of rapid withdrawal of the drug, and temporary substitution of another hypnotic, e.g. chloral hydrate or paraldehyde to promote composure and sleep. Adequate institutional nursing care, psychiatric therapy and general measures directed to restoring good physical health are essential aspects of the treatment of the morphine addict. Many, if not all, morphine addicts have basically inadequate personalities and relapses are common after apparently successful therapy.

**CLINICAL USES.** The essential indication for morphine is severe pain and the signs of acute distress which are a common accompaniment. For example, morphine is nearly always needed in myocardial infarction, the terminal stages of painful neoplastic disease, renal or biliary colic, after surgical operation, and in certain other acute illnesses. It should be administered only with great caution if there is attendant respiratory disease, because of the selective depressant action of morphine on the respiratory centre. Acute left ventricular failure with pulmonary oedema responds very well to the administration of morphine, because of its central sedative effect on the anxious patient. Morphine produces obstetrical analgesia without interfering with uterine contractions, but the infant in utero is susceptible to morphine and neonatal asphyxia may develop. When given prior to general anaesthesia morphine relieves pain and anxiety, allowing a smoother and more rapid induction. Opium preparations are valuable in the symptomatic treatment of diarrhoea, but these should only be prescribed after the removal of any irritant or poison from the bowel by purgation.

Morphine is usually administered at 4-hourly intervals by

subcutaneous or intramuscular injection of Morphine Sulphate in a dose of 8–20 mg. One half of the dose may be given intravenously to relieve acute severe pain, especially where there is peripheral vascular stasis as in shock (p. 252). Opium preparations used in the treatment of diarrhœa are Tincture of Opium in a dose of 0.3–2 ml., Aromatic Powder of Chalk with Opium—dose 0.6–4 G. and Powder of Ipecacuanha and Opium (Dover's powder) the dose of which is 0.3–0.6 G. Opium is prescribed as a cough sedative in Camphorated Tincture of Opium (Paregoric), the dose of which is 2–4 ml.

*Papaveretum* (Omnopon). This is a mixture of the soluble hydrochlorides of opium alkaloids in the proportions which occur naturally. It is a brown powder containing about 50 per cent morphine. The usual dose is 20 mg. and it can be given parenterally or orally. It is used for similar purposes to morphine and there is no evidence that its side-effects are less marked than those of morphine.

“*Nepenthe*.” *Nepenthe* is a proprietary preparation resembling tincture of opium. It contains 0.84 per cent of morphine (about 20 mg. in 3 ml.); the dose of “*Nepenthe*” is 0.3–2.6 ml.

*Codeine* is methylmorphine. It has about one-tenth the depressant powers of morphine upon the sensory area of the cerebrum, and is therefore less effective in relieving pain or in promoting sleep. Codeine is also less powerful than morphine as a depressant of the respiratory and cough centres, but it has an advantage in that the dose of codeine can be increased in order to relieve cough without causing narcotic effects. Nausea and vomiting are less common than after morphine but constipation is often troublesome. Large doses of codeine may cause restlessness and increased reflex excitability of the spinal cord: the action resembles that of strychnine; in human subjects it is apt to occur only in infants, but as codeine is rarely prescribed for infants, the matter is one of merely academic interest.

Tolerance to codeine may develop after prolonged and repeated administration of the drug. Cases of addiction have occurred but they are relatively rare. Codeine is commonly prescribed for its

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cough-suppressant action, either as the free alkaloidal base, in a dose of 10–60 mg. or as one of its soluble salts—codeine phosphate or sulphate. Compound Codeine Tablet contains 8 mg. of codeine phosphate and 0.25 G. of each of acetylsalicylic acid and phenacetin.

*Diamorphine Hydrochloride* (Heroin). This is diacetylmorphine: its actions resemble those of morphine but heroin has a more powerful effect on the sensory area of the cerebrum and it is about five times more depressant to the respiratory centre. The potency of heroin is reflected in the smallness of the dose—about a quarter of the dose of morphine. Again, side-effects such as nausea, vomiting and constipation are comparatively rare after the administration of heroin. It must be emphasised that heroin is a most powerful drug of addiction and this constitutes the main hazard in its clinical use. Intense euphoria occurs and the heroin addict rapidly develops an overwhelming craving for the drug. With rare exceptions the use of heroin should be reserved for relief of pain and restlessness in the terminal stages of fatal disease. The dose is 5–10 mg.

*Papaverine Hydrochloride*. Papaverine is one of the *isoquinoline* group of alkaloids of opium and it has been synthesised. Therapeutic doses have no narcotic action although very large amounts may cause drowsiness. It has a direct relaxant effect on certain smooth muscle cells, especially those of the coronary, pulmonary and the larger peripheral arteries. This action is more apparent when the arteries are in spasm. Papaverine increases the refractory period of cardiac muscle and reduces the conductivity in both auricles and ventricles. Overdosage may cause extrasystoles or heart-block.

Papaverine is given intravenously in cases of peripheral arterial embolism in order to promote dilatation of the collateral vessels. It has been used orally to promote dilatation of the coronary arteries in angina pectoris, but it is much less effective than glyceryl trinitrate. The dose of papaverine is 0.12–0.25 G. and in many cases it is important to give full doses in order to achieve therapeutic effects.



## DILLING'S CLINICAL PHARMACOLOGY

*Nalorphine* (N-Allylnormorphine; "Lethidrone") is a semi-synthetic substance which is closely related in chemical composition to morphine. When it is given parenterally to man, nalorphine antagonises many of the effects of morphine and its derivatives; the effect on narcosis is not conspicuous. Nalorphine is consequently of great value in the treatment of acute morphine intoxication; the intravenous injection of 10 mg. will restore both the rate and depth of breathing to normal within a few minutes in a patient with moderate respiratory depression. Should more of the drug be required, the 10 mg. dose may be repeated at 5-minute intervals to a total of 40 mg. Hypotension, if present, is also relieved. Nalorphine also relieves the respiratory depression caused by codeine, pethidine and methadone, but it is not effective when the respiratory centre in the medulla has been depressed by a barbiturate or other sedative. When morphine has been used to produce obstetrical analgesia, the intravenous injection of nalorphine immediately prior to delivery reduces the risk of neonatal respiratory depression. Nalorphine may be used in the diagnosis of morphine addiction. Subcutaneous injection of 15 mg. of nalorphine to a morphine addict produces the characteristic acute abstinence syndrome (p. 254) within thirty minutes.

The mode of action of nalorphine against morphine is obscure. On a chemical basis, it might appear to be one of substrate competition, but nalorphine also antagonises many of the effects of pethidine and methadone, neither of which has a chemical structure related to that of morphine.

### PETHIDINE

Pethidine is a synthetic piperidine derivative with some of the pharmacological actions of morphine and atropine. Its principal action is to produce analgesia, which it does less effectively than morphine. The site of the analgesic action is central, probably in the cerebral cortex and diencephalon. Visceral pain is more effectively relieved than that originating in skeletal structures. Pethidine has only a weak hypnotic action, and this is an advantage over morphine in that the analgesic dose can be increased without producing narcosis. Toxic doses of the drug produce central excitation rather than drowsiness. Therapeutic doses

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may cause transient mild depression of the respiratory centre, especially if the drug be given intravenously, but this action is much weaker than that of morphine. Toxic doses cause respiratory depression which can be relieved by nalorphine (p. 258).

Pethidine has a weak relaxant action on smooth muscle of the bronchi and gastro-intestinal tract: this is due principally to a direct effect on the muscle cells; the atropine-like action on the parasympathetic nerve endings is very weak. Pethidine causes spasm of the sphincter of Oddi, and this effect is also relieved by nalorphine. It is a valuable drug in obstetric practice: it is a powerful analgesic but it has no harmful effects on the uterine muscle at full-term, and—in contrast to morphine—it rarely produces significant depression of the respiratory centre in the newly born infant. On the cardiovascular system, pethidine in therapeutic doses usually has no untoward effects although in a few ambulant patients it may produce lightheadedness and syncope as a result of bradycardia and hypotension—which are central vagal effects.

Pethidine is readily absorbed from the gastro-intestinal tract and following parenteral injection. It is rapidly inactivated in the liver, only 10 per cent of the drug being excreted in the urine. It crosses the “placental barrier” freely.

Pethidine Hydrochloride is administered 4-hourly either orally or by intramuscular injection. It may be given intravenously when a rapid effect is desired. When it is injected too superficially it causes local irritation and pain. For ordinary purposes, the dose is 25–100 mg.—the parenteral dose usually being half of the oral one. After repeated administration tolerance develops. In general addiction to pethidine is less common than addiction to morphine. Occasionally, however, the degree of euphoria produced by pethidine is so intense that for the individual patient the hazard of addiction may be very great.

## METHADONE

Methadone (Amidone, “Physeptone”). Methadone Hydrochloride is a synthetic analgesic drug which is as potent as morphine, but it is much weaker in its narcotic action—and not infrequently this is an advantage. Methadone has a depressant effect on the respiratory centre which is greater than that of

pethidine but less than that of morphine. The selective action of this drug on the cough centre is notable—approximating to that of diamorphine: it is therefore a valuable cough-suppressant, but should not be used in the routine treatment of chronic respiratory illness as it is a drug of addiction. The depressant effect on the respiratory centre renders it unsuitable for use in obstetrical analgesia as it readily passes through the placenta and may cause respiratory difficulty in the newly born infant. Methadone has a weak morphine-like action on the alimentary canal. The effect on the cardiovascular system is similar to that of pethidine.

Methadone is readily absorbed from the gastro-intestinal tract and also after intramuscular injection; it can be administered intravenously. It is rapidly inactivated in the liver, and therefore fairly frequent (4-hourly) administration is necessary in order to maintain its analgesic effect.

In a dose of 2.5-10 mg. orally or 10 mg. intramuscularly or intravenously, methadone is used as an analgesic in many painful illnesses. The absence of drowsiness—which is a virtue in this drug on many occasions—is a disadvantage if sedatives are required as a preliminary to operation and the induction of general anaesthesia; here morphine is usually the drug of choice. In combating a useless cough—the so-called antitussive action—the oral dose of methadone is 1.5-2 mg.

## SALICYLATES AND OTHER ANALGESICS

### ANALGESICS

Analgesics are drugs which relieve pain by their central action on the brain. They are to be distinguished from *counter-irritants* (p. 427) which may relieve pain by a local effect on the skin; from *local anaesthetics* (p. 165) which make sensory receptors insensitive; and from *general anaesthetics* (p. 187) which act by making the patient unconscious.

In medical practice a considerable variety of analgesics are used. A selection of these drugs are considered in this chapter. The best-known preparation is ASPIRIN or acetylsalicylic acid. The parent substance—salicylic acid—though possessing analgesic effects, is rarely or never used for this purpose because it has an irritant

action on the stomach. The properties of salicylic acid which account for this effect on the gastric mucosa and on other tissues are nevertheless of great interest and importance in other fields of therapeutics. Further consideration of salicylic acid is accordingly deferred (p. 275) in favour of a brief discussion of those salicylates which are used for their analgesic effects.

From time immemorial, willow bark (*Salix alba*) has been used empirically to give relief of symptoms in feverish illnesses. Our knowledge of the active principle—the glycoside salicin—dates from 1827 (Leroux), and from the work of Piria (1838) who prepared salicylic acid from salicin. Salicylic acid was first synthesised in 1860 (Kolbe and Lautemann); and the esters of salicylic acid such as acetylsalicylic acid (aspirin), phenyl salicylate and sodium salicylate were subsequently investigated pharmacologically and have been introduced into therapeutics. These drugs have been of immense importance in medical practice and they are still widely used to relieve pain and to alleviate the symptoms associated with certain types of pyrexial illness.

The salicylates that are used internally have much in common in their pharmacological actions. They have been well described as antipyretic analgesics. There are, however, quantitative differences in the various systems of the body which justify the clinician in his practice of reserving the individual salicylates for particular therapeutic purposes. In general the "salicylate effect" can be achieved by means of aspirin, but there are occasions when the practitioner prefers to use sodium salicylate. The reason for this preference is discussed below.

The remarkable antipyretic action of the salicylates can be understood by regarding the temperature-regulating centre in the mid-brain as a thermostat. In the febrile state the centre is "set" at a high level; and many of the disagreeable sensations at the onset of "fever" are attributable to events calculated to restore equilibrium between *heat production* and *heat loss*. These matters are discussed in detail in standard works on applied physiology. The most obvious effects are shivering and pallor—favouring heat production and conservation—and later, increased heat loss through congestion of the skin and a raised skin temperature, sweating, and the consequences of dehydration (malaise, thirst,

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headache, oliguria, etc.). Salicylates re-set the temperature-regulating centre at its "normal" level. This results in a further utilisation of physiological mechanisms to intensify heat loss and to re-establish equilibrium between heat-production and heat-loss at the new setting of the thermostat. Provided that salicylate therapy is supported by appropriate general measures such as ensuring adequate fluid intake, the antipyretic action is highly beneficial.

The *analgesic action* of the salicylates is due to depression of transmission of pain impulses through the thalamus; there is no impairment of cortical function. Acetylsalicylic acid is a more potent analgesic than sodium salicylate but both of these are much weaker than morphine in their analgesic activity. The salicylates (more specifically, aspirin) are prescribed for the relief of pain of the aching type which is common in diseases of musculo-skeletal structures, but they are also useful in headache and in dysmenorrhœa; and they may be of limited value in toothache associated with minor degrees of dental caries.

### SODIUM SALICYLATE

Sodium salicylate is a specific remedy in the symptomatic therapy of acute rheumatic fever. *In full doses\** it reduces the temperature and relieves the pain, redness and swelling of the joints within 24–48 hours. The action is so reliable that it has been applied by the clinician as a therapeutic test of his diagnosis. It is not known how salicylates bring about this dramatic improvement in acute rheumatic fever. There is no clear proof that salicylates offer a *cure* for acute rheumatism in the sense that an infection may be eradicated by a specific remedy, for the treatment certainly does not reduce the patient's liability to cardiac complications—which are classic sequelæ to this disease.

The drug is given orally in a dose of 2 G. every 4 hours with an equal amount of sodium bicarbonate. The object of giving sodium bicarbonate is to neutralise the gastric hydrochloric acid: thus the amount of salicylic acid set free in the stomach is reduced to a minimum and there is less chance of causing irritation—with

\* The quantities mentioned are for general guidance only, and in some instances only approximations are given.

## ANALGESICS

nausea and vomiting. On balance the advantage is worth while, but the use of sodium bicarbonate tends to hasten the excretion of sodium salicylate and militates somewhat against the maintenance of adequate salicylate levels in the blood and other tissues. Intensive treatment with full doses is continued until early signs of overdose ("salicylism") occur. The dose is then reduced to 1-2 G. every 6 hours for a further three weeks, after which the drug is withdrawn gradually if the clinical condition warrants this.

In addition to their being antipyretic and analgesic agents, the salicylates promote the renal excretion of uric acid. They do this by lowering the renal threshold for uric acid. This action has been applied in the treatment of chronic gout, as sodium salicylate is much less toxic than cinchophen (p. 273).

Many of the desirable pharmacological actions of the salicylates can be produced without side-effects that are of practical importance. Excessive doses, however, produce constitutional upsets which are at first mild but which may become serious. These toxic effects are collectively called the state of *salicylism*. Even in therapeutic dosage, salicylates produce appreciable hyperventilation which increases respiratory minute volume; this is attributable to reflex stimulation of the respiratory centre by impulses acting on peripheral receptors innervated by afferent vagal fibres. Plasma salicylate levels above 30 mg. per cent are usually associated with hyperventilation, and when the level rises to 50 mg. per cent severe dyspnoea ensues. The hyperventilation tends to produce a respiratory alkalosis, for which compensation is usually adequate: the serum carbon dioxide tension is reduced, the serum chloride is usually elevated, and the serum pH is either unchanged or tends to be increased. Acidosis may follow. The metabolic disturbances producing this acidotic state are complex but it is probably partly due to the presence of the salicylic acid radicle.

The cardiovascular system is not directly affected by therapeutic doses of salicylates, but toxic amounts cause central vasomotor paralysis. As already stated, the salicylates may cause gastric irritation with nausea, epigastric discomfort and even hæmatemesis. The release of salicylic acid from sodium salicylate may produce gastric irritation and there are many reports of acetylsalicylic acid causing gastric erosions and on occasion severe gastric hæmorrhage.

It is possible that this mucosal reaction constitutes a local idiosyncrasy to acetylsalicylic acid, but in order to minimise this hazard, the drug should be given as a powder (the tablet crushed), taken after food and it should be followed by a draught of water. The soluble salts of acetylsalicylic acid are possibly less likely to give rise to gastric irritation. The nausea and vomiting which occur in acute salicylate overdosage are mainly central in origin. Large doses of salicylate such as are employed in acute rheumatic fever lower the prothrombin content of the blood; the mechanism of this action is unknown, but it may be that salicylates interfere with the utilisation of vitamin K which is necessary for the synthesis of prothrombin (p. 86).

*Toxic Effects.* Mild salicylate intoxication ("salicylism") presents with headache, ringing in the ears, slight deafness and vertigo. These symptoms may be followed by vomiting, flushing of the skin, drowsiness and confusion; and hyper-ventilation becomes obvious. The headache and tinnitus may be associated with congestion of the peripheral vessels, and, at this stage, nausea and vomiting are caused mainly by central stimulation. Even when sodium salicylate is administered intravenously this may be followed by nausea and vomiting—providing proof of the importance of central stimulation. With continued excessive dosage, more severe signs of salicylate poisoning develop. Restlessness, delirium, convulsions and coma may ensue. Various skin eruptions may appear, and exaggeration of the respiratory alkalosis and disturbance of serum electrolyte levels follow. Death usually results from respiratory failure.

Signs of *idiosyncrasy* to salicylate may be seen following the first doses of the drug. It most commonly occurs after the use of aspirin, and the allergic reactions take the form of angioneurotic œdema, urticaria, or acute bronchospasm with wheezing.

*Absorption and Excretion.* Absorption of salicylates takes place almost entirely in the upper small intestine; a trace is absorbed from the stomach. Appreciable quantities can be detected in the blood within 30 minutes of ingestion, and maximum concentrations are found within 2 hours. Intestinal absorption of acetyl-

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salicylic acid is hastened by the simultaneous administration of sodium bicarbonate. Excretion of salicylate in the urine is relatively slow; although it begins within 15 minutes, only 50 per cent of a single dose is excreted within 24 hours and traces are still present in the urine after 48 hours. The bulk appears as unaltered salicylate and other excretion products are salicyluric acid (a compound of salicylic acid and glycine), gentisic acid, and conjugates of glycuronic and salicylic acid.

*Fate.* After absorption salicylate passes readily to all tissues and crosses the placental barrier; it is not secreted in the gastric juice. Following on therapeutic doses most of the salicylate is bound to the plasma proteins. The concentration of plasma salicylate can be lowered by alkalisation of the urine with sodium bicarbonate; the renal clearance of salicylate increases rapidly when the *pH* is raised above 7.

## PREPARATIONS

There are many forms in which salicylates may be prescribed, but the two compounds which are most commonly used are sodium salicylate and acetylsalicylic acid (aspirin).

Sodium salicylate is a less palatable and less effective analgesic than acetylsalicylic acid, and its use should be restricted to the treatment of acute rheumatic fever. It can be dispensed as Sodium Salicylate Mixture Strong which contains 1·3 G. in 15 ml. The daily requirement in acute rheumatic fever is usually 6–12 G. given orally in divided doses with draughts of water after meals.

Acetylsalicylic Acid (Aspirin) may be prescribed as tablets which contain approximately 150, 300 or 500 mg. The tablets should preferably be taken crushed after food or given in the soluble form—Acetylsalicylic Acid Soluble Tablets (aspirin compounded with citric acid and calcium carbonate). There are many compound tablets which contain aspirin; one is Acetylsalicylic Acid Compound Tablet of the British Pharmaceutical Codex ("APC Tablet") which contains caffeine 32·5 mg., phenacetin 162 mg. and acetylsalicylic acid 227 mg.; another is Codeine Compound Tablet which contains codeine phosphate 8·1 mg., and acetylsalicylic acid and phenacetin (p. 266) of each, 260 mg. The usual



dose of acetylsalicylic acid for an adult is 600 mg. but as a single dose it is often 1 G.

METHYL SALICYLATE is a colourless liquid with a characteristic odour, miscible with fats and oils. It is popularly used as a counter-irritant (p. 427) and rubefacient in the treatment of muscular rheumatism or "fibrositis". It may be prescribed as Methyl Salicylate Liniment containing 25 per cent v/v of the drug, usually in pea-nut oil; Methyl Salicylate Ointment contains 50 per cent methyl salicylate in white beeswax and hydrous wool fat.

Oil of Wintergreen, which is chiefly methyl salicylate has the same actions and uses.

There are two derivatives of coal-tar which have therapeutic uses as analgesics and antipyretics comparable to those of the salicylates: these are Phenacetin (Acetophenetidin,) and Acetanilide.

PHENACETIN has analgesic potency similar to that of acetylsalicylic acid and it also acts at the level of the thalamus without depression of cortical function. Phenacetin is used therapeutically for the relief of the pain in headache, the aches and pains of chronic rheumatism, arthritis, dysmenorrhœa and such disorders. It is not effective in relieving severe visceral pain: this responds only to opium and related drugs (p. 245). Phenacetin is found in many official and proprietary preparations combined with acetylsalicylic acid, codeine or caffeine in varying amounts. Phenacetin is a powerful antipyretic, achieving this action through the temperature-regulating centre in the hypothalamus. When administered during fever, there follows increased loss of body heat and profuse perspiration develops as a consequence of dilatation of the peripheral blood-vessels in the skin. Phenacetin has no specific activity in the treatment of acute rheumatic fever.

*Toxic Effects.* In therapeutic doses, phenacetin has no harmful effect on heart, liver or kidney tissues. An important toxic effect however is methæmoglobinæmia and sulphæmoglobinæmia which may occur during prolonged therapy with phenacetin (see below). Lethal doses cause central respiratory depression.

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**Absorption, Fate and Excretion.** Phenacetin is rapidly and almost completely absorbed from the upper small intestine, and peak levels appear in the blood one to two hours after ingestion. Phenacetin is de-ethylated to N-acetyl-*p*-aminophenol which is rapidly excreted in the urine, partly unchanged, but most of it is conjugated with sulphuric acid or glycuronic acid. A small fraction of phenacetin is de-acetylated in the body to form *p*-phenetidin which is the precursor of an unknown substance which converts hæmoglobin to methæmoglobin and sulphæmoglobin. N-acetyl-*p*-aminophenol causes neither methæmoglobinæmia nor sulphæmoglobinæmia. Phenacetin is taken orally: Phenacetin Tablet contains 325 mg. The dose is 300–600 mg. Phenacetin and Caffeine Tablets each contain phenacetin 260 mg. and caffeine 65 mg. Other available preparations containing phenacetin are listed with those of aspirin.

**PARACETAMOL** (N-acetyl-*p*-aminophenol; "Panadol"). The degradation product of phenacetin in the body is itself analgesic and antipyretic. Its pharmacological action is similar to that of phenacetin. Paracetamol is less toxic in that it does not produce methæmoglobinæmia or sulphæmoglobinæmia and it is a useful remedy for the relief of moderately severe pain. This preparation is taken orally as a tablet containing 0.5 G.

**ACETANILIDE** (Antifebrin) is obsolete. It has been superseded because, notwithstanding its great potency as an analgesic-antipyretic, it is so toxic that its therapeutic use can no longer be justified. In any discussion of the merits of a particular drug, due regard must be paid to conditions existing at the time when the drug was introduced. In its day (introduced in 1886) acetanilide represented an important advance in therapeutics; its introduction was a significant event in the history of medicine, because it gave a hint of the extraordinary developments in pharmacology which have emanated from the ingenuity of the synthetic chemist. Further, it must be admitted that in the hands of a careful practitioner, acetanilide might still be used effectively and harmlessly, because the toxic effects are rarely seen except after prolonged administration. A person who resorts to a single dose of

acetanilide for the relief of headache at intervals of a few weeks will be none the worse for the experience unless there is a state of idiosyncrasy; but daily self-medication with acetanilide as a "headache powder" for months or years is fraught with serious danger. It is therefore true to say that, in present circumstances the elimination of acetanilide from therapeutics is in the best interests of the public.

In the same category as acetanilide are two other drugs which were commonly employed in the past as analgesics and antipyretics, but which—in view of their toxicity—are no longer the preparations of choice for therapeutic use. They are phenazone and amidopyrine—derivatives of phenylpyrazolone.

**PHENAZONE** (Antipyrin) is phenyldimethylisopyrazolone. Its pharmacological actions are similar to those of phenacetin. Peak levels in the blood are found 1–2 hours after ingestion. Phenazone is distributed so evenly in the body tissues in proportion to their water content that the drug has been used experimentally to measure total body water. Phenazone is slowly eliminated from the body: about 40 per cent is oxidised and 5 per cent is excreted unchanged in the urine; the fate of the remainder is unknown. Phenazone does not cause methæmoglobinæmia but may cause skin eruptions which are characteristic in their distribution and slow to disappear. The dose of phenazone is 0.3–0.6 G.

**AMIDOPYRINE** is dimethylaminophenyldimethylpyrazolone. This drug is the most powerful analgesic of the group. However, it occasionally causes agranulocytosis—a complication which is always serious and which may be fatal. In view of this hazard, amidopyrine should not be prescribed, either alone or in combination with other drugs.

**PHENYLBUTAZONE** ("Butazolidin") is 4-butyl-1:2-diphenylpyrazolidine-3:5-dione. It is a white crystalline powder which is almost insoluble in water. Phenylbutazone has analgesic and antipyretic actions similar to those of amidopyrine. Early reports suggested that it gave remarkable results in the treatment of rheuma-

toid arthritis. However, further clinical trials have not provided convincing proof that phenylbutazone is superior to aspirin and other analgesics in this condition. This aspect of the subject is discussed further in the final paragraph of this section (p. 271). It greatly increases the output of uric acid in the urine, and this explains its successful application in the treatment of acute or chronic gout, but less toxic compounds such as probenecid (p. 274) or sodium salicylate (p. 265) are to be preferred in the treatment of gout. Renal excretion of sodium and chloride is reduced during therapy with phenylbutazone. This results in an increase in plasma volume which in turn may precipitate congestive cardiac failure in some patients with heart disease.

*Toxic Effects.* Phenylbutazone is poorly tolerated and gives rise to a wide variety of toxic side-effects. Untoward reactions occur in some 25-40 per cent of patients and therapy must be discontinued in 10-15 per cent. In addition to the increase in extracellular fluid described above, nausea, vomiting, epigastric pain, diarrhoea and skin rashes are common. Insomnia, blurring of vision, vertigo and stomatitis have also been observed. The most serious toxic effects are reactivation of peptic ulceration with hæmorrhage; and also agranulocytosis and aplastic anæmia have been reported. A patient may have an idiosyncrasy to phenylbutazone and in these circumstances toxic reactions may appear after the first dose of the drug.

In view of the known toxic effects of phenylbutazone, certain recommendations can be offered to the clinician. The drug is contra-indicated in patients with cardiac, renal or hepatic disease, and it should be avoided in those with a history of peptic ulceration. Phenylbutazone should not be prescribed where there is a previous history of a blood dyscrasia or of drug allergy.

*Absorption, Fate and Excretion.* Phenylbutazone is well absorbed from the small intestine. It is slowly metabolised and excreted, but the details of its fate in the tissues are not fully known.

Phenylbutazone is available as tablets (100 mg. and 200 mg.) for oral administration; it should be taken after meals in order to reduce the risk of gastric irritation. It is also available for intra-

muscular injection in a concentration of 200 mg. per ml. The total daily dose is 200-400 mg. in divided doses, but after the first few days the dose should be tapered to the minimum quantity that controls symptoms. There is little doubt that the reputation of this drug has suffered from its being given in unnecessarily large doses when it was first introduced for clinical use.

It has been stated above that, notwithstanding early claims made on behalf of phenylbutazone in the treatment of rheumatoid arthritis, this drug has little or no advantage over aspirin. An opinion of the relative merits of two drugs must take into account the pharmacological actions, therapeutic effectiveness, toxicity and ease of administration. It is then usually apparent that on balance it is preferable to use one drug rather than another. A physician is of course entitled to depend on his personal experience, but he is bound to be influenced by the considered opinions of his colleagues and by publications appearing in the medical press. In particular he notes the results of well-designed clinical trials. The general principles of such investigations are discussed briefly in Chapter 23. Here it is intended merely to draw attention to one aspect of the subject.

The results of a clinical trial carried out on a drug seldom justify the assertion that the substance has no therapeutic value in any patient to whom it has been given. (If there were no *prima facie* case for using the drug in a particular disease, few clinicians would be disposed to undertake the work involved in a thorough clinical trial.) A "negative" conclusion to a clinical trial is nearly always expressed in guarded terms: it is stated that the evidence that has emerged from the investigation does not warrant the opinion that the drug has therapeutic value. This statement is necessarily founded on a review of data collected from groups of experimental subjects under conditions defined by the investigators. It is not incompatible with the possibility that a very small proportion of the patients did in fact derive direct benefit from the use of the drug. Conditions peculiar to the state of one or two patients may conceivably create a "special experiment" within the framework of the larger one; but their genuine cause-and-effect benefits may easily fail to emerge in the statistical handling of the whole mass of data collected from the large groups of patients. These consid-

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erations appear to be applicable to the effects of phenylbutazone—and doubtless to the assessment of many other drugs. A practitioner may be much impressed by the favourable response obtained in an individual patient suffering from rheumatoid arthritis when treated with phenylbutazone. The physician may have this experience, despite a well-founded opinion that *in general* the benefits conferred by phenylbutazone on patients with rheumatoid arthritis are no greater than the benefits conferred by salicylate therapy. The “exceptional patient” who reacts in this gratifying manner to the use of phenylbutazone calls for closer study. He may be willing to co-operate in a series of clinical trials designed for use on an individual patient. Thus he may demonstrate his ability to identify courses of treatment with (a) phenylbutazone, (b) inert substances and (c) aspirin—given in series but selected at random; and precautions may be taken to keep the patient and all his attendants in ignorance of the nature of the treatment until the set of tests has been completed.

In brief, the results of phenylbutazone treatment in rheumatoid arthritis cannot be disposed of by a generalisation. As in all forms of drug therapy, the outcome of a clinical trial is extremely valuable in indicating the probability or improbability of achieving therapeutic benefits. Nevertheless, allowance must be made for the fact that the statistical analysis is concerned with data, whereas the doctor is concerned with patients; and he must be sufficient of a biologist not to ignore the oddities of clinical practice, even when these are in danger of being swept away in a sea of statistics.

## DRUGS USED IN GOUT

COLCHICINE is an alkaloid obtained from the corm and seeds of *Colchicum autumnale*, a plant so named because it was harvested in Colchis in Asia Minor. It is a pale-yellow powder, darkening on exposure to light. The BPC Tablet contains 0.27 mg. of colchicine.

Colchicine is a specific remedy for acute gout. The mechanism of its action is unknown. It has no analgesic action. It does not influence the blood levels of uric acid, nor does it act as a diuretic promoting the excretion of urates. In practice, however, the relief

obtained in acute gout is dramatic: with adequate oral dosage—1 mg. 2-hourly of colchicine to a total of 4–8 mg.—the crippling symptoms of the acute attack are abolished in 95 per cent of patients. Pain, redness and swelling subside in about 12 hours and have usually disappeared completely within 48 hours. The course of therapy should not be repeated until an interval of 3 days has elapsed, as poisoning may develop from cumulation of the drug. In therapeutic doses colchicine exhibits no other significant pharmacological actions, but it is known to arrest cell-mitosis—both in plants and in animals. This may account for the temporary leucopenia which occurs in patients receiving colchicine. It has provided a justification for assessing the value of the drug in reducing the production of lymphocytes in cases of leukaemia.

*Toxic Effects.* Toxic amounts of colchicine may cause agranulocytosis or aplastic anaemia. In acute poisoning an unexplained latent period elapses between ingestion of the drug and the appearance of toxic symptoms. The first to appear are usually those of severe gastro-intestinal irritation, with colic, repeated vomiting and hæmorrhagic watery diarrhoea; these effects may be related to excretion of the drug into the alimentary tract, for they are sometimes seen also after *parenteral* administration of colchicine. Severe tissue damage may also occur in the kidney, and oliguria and hæmaturia may then develop. Toxic doses produce motor and sensory depression of the central nervous system presenting as an ascending paralysis culminating in fatal respiratory arrest.

*Absorption, Fate and Excretion.* The fate of colchicine in man is unknown, but from studies in animals and from the signs of toxicity in human patients it is probable that excretion takes place mainly through the liver, entering the intestine in the biliary secretion; a smaller quantity is excreted in the urine.

The treatment of *acute gout* by means of colchicine has already been mentioned. The patient with *chronic gout* who is subject to frequent acute exacerbations may be able to prevent these by taking 0.5–2.0 mg. of colchicine orally on alternate days. Because of toxic effects and the liability of the drug to cause fluid depletion and shock, colchicine must be prescribed with great care in

elderly patients or in those with cardiac, renal or gastro-intestinal disease.

*Preparations.* There are several galenical preparations of colchicum but the alkaloid Colchicine is the preparation of choice. The single oral dose of colchicine is 0.5-1.0 mg. and the total dose is 2-8 mg.

CINCHOPHEN is phenyl quinoline carboxylic acid. It is a white powder, darkening in the light; it is almost insoluble in water. Its pharmacological actions resemble those of the salicylates: it is classed as an analgesic-antipyretic but in practice the toxicity of cinchophen precludes its general use for these purposes. The main action of cinchophen is to increase the urinary excretion of uric acid by inhibiting active reabsorption of urate in the renal tubules; in this respect it resembles salicylates (p. 263) and probenecid (p. 274). This selective action of cinchophen on uric acid excretion is, however, much more powerful and more rapid than that of salicylates: the increased excretion reaches a maximum in 3 hours and then declines, but repeated administration over 2 days maintains a high rate of elimination; this naturally causes a simultaneous fall in the level of uric acid in the blood, but occasionally such a fall is delayed. Cinchophen, unlike the salicylates, does not stimulate respiration, nor does it affect the levels of serum electrolytes.

*Toxic Effects.* Cinchophen may cause many of the symptoms of "salicylism" (p. 264) but the most important toxic effect of this drug is on the liver. Following on the first or any subsequent dose, liver necrosis may occur. This is always a serious complication and may be fatal. There is no way of detecting the patients who are likely to develop these acute degenerative changes in the liver; and once the condition has begun, the symptoms and signs develop relentlessly, even though administration of cinchophen is immediately stopped. Cinchophen should not be prescribed for patients with hepatic or renal disease. Because of the risk of hepatic necrosis, cinchophen is seldom employed in the treatment of chronic gout; probenecid (p. 274) is preferred.



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**Absorption, Fate and Excretion.** Cinchophen is absorbed satisfactorily from the small intestine and is widely distributed in the body tissues. It is almost completely metabolised; only about 2 per cent is excreted in the urine.

Cinchophen is given orally as tablets containing 0.3 or 0.5 G. of the drug. In the treatment of chronic gout it may be prescribed as 0.5 G. thrice daily *for three days only* as a course of treatment; each dose is followed by a large draught of water. Simultaneously a mixture of sodium bicarbonate and potassium citrate is given to render the urine alkaline; this helps to prevent precipitation of the uric acid in the renal tubules.

PROBENECID ("Benemid") (see also renal tubular blocking agents, p. 52) is a derivative of benzoic acid. It interferes with the renal elimination of penicillin (p. 439) and para-aminosalicylic acid (p. 483). Probenecid greatly increases the renal excretion of urates by inhibiting their reabsorption in the renal tubules; the cellular mechanism which results in the inhibition of urate reabsorption is not understood. Probenecid is the most effective drug known for promoting excretion of uric acid in the treatment of chronic gout. It should not be used alone in *acute* gout: here colchicine should be prescribed to control the acute episode, but it can be supplemented by giving probenecid. Salicylates should not be given with probenecid in the treatment of gout as they interfere with the action of probenecid in promoting uric acid excretion. A daily dose of 0.5 G. of probenecid is given orally for one week, and the dose is then increased to 0.5 G. twice daily. The total duration of therapy is controlled by serial estimations of the blood uric acid. Throughout this course of treatment the urine should be kept alkaline (see above).

**Toxic Effects.** Toxic effects are uncommon although side-effects, including nausea and minor skin eruptions, have been reported among patients receiving probenecid.

**Absorption, Fate and Excretion.** Probenecid is rapidly absorbed from the small intestine. Peak blood levels are obtained about two hours after ingestion of the drug. Urinary excretion of free

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probenecid is low; the drug is slowly conjugated in the body with glucuronic acid.

The drug is available as a tablet containing 0.5 G. for oral administration.

**SALICYLIC ACID.** The status of salicylic acid is mentioned earlier in this chapter (p. 261). From a chemical viewpoint, the parent substance would take priority. The pharmacologist would also discuss the actions of the salicylates on the organism in terms of salicylic acid. The clinician, however, makes a different approach: he is bound to take into account the factual statements of both the chemist and the experimental pharmacologist, but his concept of the action of *salicylic acid* is inevitably modified by what he sees of its effect when it is used therapeutically in man. A suitable preparation of salicylic acid is keratolytic; it dissolves the cells of the stratum corneum. Thus Salicylic Acid (12 per cent in Flexible Collodion) is applied to corns and warts and it slowly destroys them without causing a local inflammatory reaction; as the Paste of Zinc Oxide and Salicylic Acid, it may be used to clear the skin of "scales"—caused by excessive proliferation of the stratum corneum; in the Compound Dusting Powder of Salicylic Acid (3 per cent) its effect on the skin surface is inimical to the growth of fungi and bacteria. Its low solubility in water (1 in 550) limits its use as a quick-acting antiseptic, though under ideal conditions it is a more powerful antiseptic than phenol. A trace of salicylic acid in foodstuffs inhibits bacterial growth, but the use of the drug for this purpose is forbidden—on the principle that producers of dirty food should not escape detection by resorting to antiseptics. Salicylic acid is readily soluble in alcohol, however, and a 4 per cent solution can be used in restricted areas of the body to prevent sweating.

The pattern of therapeutic applications indicates clearly enough why salicylic acid as such is never given internally, and why it must be "fixed" as a salicylate when the constitutional effects of the drug are required as an antipyretic or analgesic (p. 262).

## CHAPTER 9

# HISTAMINE AND ANTIHISTAMINICS

## HISTAMINE

### CHEMISTRY AND DISTRIBUTION

HISTAMINE is 4-2'-aminoethyliminazole. It plays a part in many physiological processes but its therapeutic applications are remarkably limited. It has been found in all body tissues (though it is absent from pancreatic juice), and it occurs in many plants such as nettles and tomatoes. The concentration in different organs varies with the species. In man histamine occurs mainly in the skin, lungs, gastro-intestinal tract and mast cells. The histamine content of the central nervous system is low except in and around the posterior pituitary where the concentration is high. The blood histamine is 1-8 micrograms per 100 ml., and most of this is in the eosinophils.

In 1907 Windaus and Vogt synthesised histamine from imidazole-propionic acid. Three years later Barger and Dale isolated it from ergot and in the same year Dale and Laidlaw described its pharmacology. In mammals, however, histamine is formed by carboxylation of histidine, both in the bowel lumen and in the tissues. There is no clear proof that histamine is ingested as a "vitamin". The thyroid gland is the only endocrine organ known to influence histamine production. Skin histamine may be increased in hyperthyroidism and depleted in myxœdema. Cortisone has been shown to depress histamine production in experimental animals. This may explain its clinical effectiveness in such conditions as hay fever and asthma, as well as its inhibitory effect on the primary inflammatory reaction in which histamine has an important role.

Tissue histamine may be released by a variety of apparently unrelated agents. These include trauma, antigens, trypsin, bile salts and d-tubocurarine and even the antihistamines themselves.

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In dermographism histamine sufficient to stimulate gastric secretion may be liberated.

It is easy to enumerate substances known to release histamine. It is difficult to explain how they act. The main theories are (a) that histamine is released from cells or intracellular particles by destruction of the cell or by an increase in the permeability of the cell membrane; (b) that it is displaced from a loose bond with some other cell component by a chemically related compound; (c) that it is detached from intracellular protein by proteolytic enzymes. Compound 48/80 (phenylethylamine compound) is the most specific histamine liberator known. It may form a heparin-liberator complex which increases the permeability of the mast cell granule and allows the outward diffusion of histamine.

*Anaphylaxis* is a state of profound and often fatal shock which can be induced in the experimental animal. Parenteral injection of foreign protein leads to the production of antibodies and their distribution in tissue cells. A second injection of the same protein 10-14 days later causes an antigen-antibody reaction which liberates histamine. The histamine release takes place in or close to the effector cell, and this explains why antihistamines which block the effects of injected histamine do not prevent the effects of injected antigen. Although histamine release is usually invoked to explain anaphylaxis, other explanations are open to consideration: the antigen-antibody reaction may produce some other substance, or stimulate the cell directly without the mediation of an agent such as histamine.

*Allergy* is the clinical exhibition of the anaphylactic mechanism. The various allergic syndromes depend on the site, nature and intensity of the particular antigen-antibody reaction.

**FATE.** Endogenous histamine is released within the body. According to Dale intrinsic histamine is released and acts at the same place, perhaps even in the same cell, while extrinsic histamine is released at one point and acts at another. If antihistamines block only the effects of circulating histamine, this concept explains why they abolish some histamine effects and not others. Endogenous histamine is inactivated by tissue histaminase or by

intracellular binding. Exogenous histamine given parenterally is inactivated in the same way, but given orally it is acetylated in the bowel or in the liver and excreted in the urine as acetylhistamine.

**PHARMACOLOGY.** The clinical manifestations of histamine can be accounted for by three main groups of actions: on blood vessels, on smooth muscle and on certain glands.

(1) *Blood Vessels.* Histamine is a powerful dilator of capillaries. This action is independent of nerve conduction and is only partially blocked by antihistamines. Higher concentrations increase capillary permeability so that plasma diffuses into the tissues. Locally this is seen as urticaria or angioneurotic oedema; systemically as shock due to the fall in blood pressure associated with peripheral vasodilatation and massive leakage of plasma into the tissues, with the consequent reduction in circulating blood volume. Doses of histamine insufficient to produce shock cause generalised flushing and a rise in skin temperature.

The action of histamine on arterioles varies in different species, but in man dilatation occurs.

The capillary-arteriole effect of histamine is neatly demonstrated by the "triple response". Light stroking of the skin with a blunt point produces a white track due either to pressure closure of the capillaries or to active constriction. If, however, the point is applied more firmly, a red line will appear in 5-15 seconds, followed by a spreading flare and then by a weal. The red track is due to capillary dilatation, the spreading flare to arteriolar dilatation mediated by the axon reflex, and the weal to the escape of plasma through the permeable walls of the capillaries. Lewis, who first described this response, attributed it to the release of an "H-substance". It seems certain that histamine and H-substance are identical. Dermographism is a florid example of the triple response.

Histamine has no direct action on the myocardium. The tachycardia and increased cardiac output are due to the effects of widespread peripheral dilatation. The headache which sometimes follows histamine administration is attributed to dilatation of cerebral vessels and stretching of the pial and dural meninges.

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(2) Smooth Muscle. Histamine constricts the bronchioles by contraction of their smooth muscle. This action occurs in bronchial asthma, bronchitis and in cardiac asthma, but in normal people it is difficult to reproduce this action by injecting histamine. In asthma the spasm is due to the allergic release of intrinsic histamine by foreign materials such as pollen or house dust, or even by psychogenic stress. Pollen allergy was demonstrated *in vitro* on human lung resected from an asthmatic subject. The addition of pollen to the water bath containing the specimen was followed by marked bronchiolar constriction. Antihistamines did not block this response, but did prevent a similar response to added histamine.

Early beliefs that histamine stimulated uterine and gall bladder contraction have not been confirmed.

(3) Glands. Histamine is the most powerful known stimulant of the glands which secrete gastric juice. Gastric mucosa is rich in histamine and this is found mainly in the acid-producing areas close to the acid-secreting cells. At first it was assumed that it caused the secretion of pepsin as well as acid. It seems, however, that there is a slow and continuous secretion of pepsin which is independent of stimulation by histamine; and by contrast, the acid-secreting function of the gastric mucosa appears to be dependent on the presence of histamine. Extrinsic histamine released anywhere in the body by whatever method stimulates the output of hydrochloric acid. It seems to act directly on the oxyntic cells and there is no evidence for the existence of a chemical mediator. It is not antagonised by antihistamines, though the action is slightly reduced by atropine. The mode of action is not known. It may simply increase blood flow to the cell.

Histamine releases adrenaline from the suprarenal medulla. This action is of no importance in normal people but may be of diagnostic value in the presence of a phæochromocytoma, the suprarenal tumour which secretes and stores large quantities of adrenaline.

Salivary and pancreatic secretions are slightly increased by histamine.

## CLINICAL USES—

DIAGNOSTIC. (1) In the normal subject subcutaneous injection of 0.25 mg. of histamine acid phosphate is followed 15-45 minutes later by the secretion of highly acid gastric juice. In about 10 per cent of otherwise normal people no acid secretion occurs. They have what can be called a "histamine-resistant achlorhydria". If there is no acid secretion after 2 mg. of histamine ("augmented histamine test") the state of histamine-fast achlorhydria is regarded as established. It is necessary to prevent the *systemic* effects of such a large dose of histamine by giving one of the antihistamines. Demonstration of histamine-fast achlorhydria is essential to the diagnosis of Addisonian pernicious anæmia.

(2) A phæochromocytoma is an adrenal medullary tumour which in its early stages causes paroxysmal hypertension and other manifestations of adrenaline release. During a quiescent phase the diagnosis can only be suspected on the clinical history, but confirmatory evidence may be obtained by the intravenous injection of 10-25 micrograms of histamine acid phosphate. This provokes adrenaline release from the tumour so that the systolic blood pressure rises significantly and other signs of hyperadrenalism may appear. Before attempting to assess the effect of histamine an injection of physiological saline should always be given as a control. In normal subjects intravenous administration of histamine causes a slight fall in blood pressure followed by a slight rise.

(3) Histamine has been used in the estimation of circulation times. It has also been used by neurologists in certain diagnostic procedures.

THERAPEUTIC. The administration of histamine has been advocated in the treatment of many disorders including peripheral vascular disease, disseminated sclerosis, indolent ulcers of skin, migraine and Ménière's disease. Notwithstanding occasional enthusiastic reports, proof of the therapeutic usefulness of histamine preparations is still lacking.

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### PREPARATIONS

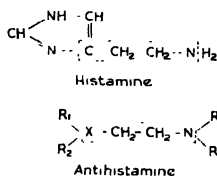
Histamine acid phosphate and histamine dihydrochloride are pure, crystalline, water-soluble preparations.

Injection of Histamine Acid Phosphate contains 1 mg. in each ml.

### ANTIHISTAMINES

Although the therapeutic benefits derived from histamine are so meagre, the search for substances to prevent or modify the allergic response has led to the introduction of valuable new remedies. Not only have potent antihistaminics been discovered, but also compounds with anti-emetic and tranquillising actions. The first aim of the pharmacologist was to synthesise substances chemically related to histamine but pharmacologically inert, for such preparations can be expected to act as efficient blocking agents—preventing the characteristic effects of histamine (see below). This ideal has not been achieved. The first antihistamines were too toxic for clinical use and later compounds, although much safer, caused side-effects which conferred on the antihistamines as a group a distinctive pharmacology. In retrospect it is clear that a number of therapeutic advances can be traced to the failure of the early research workers to produce the “perfect” blocking agent.

Fig. 1 shows the relationship between histamine and the basic molecular structure of the main antihistamines:

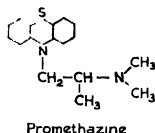


“X” is replaced either by carbon, nitrogen or oxygen.



## DILLING'S CLINICAL PHARMACOLOGY

Fig. 2 shows the structure of promethazine:



This phenothiazine derivative has potent sedative as well as antihistaminic actions, and it is the precursor of chlorpromazine (p. 222).

### MODE OF ACTION

The antihistamines are thought to act by competitive inhibition. Because of their structural similarity to histamine they are accepted by the histamine receptors in the effector cells, which are thus blocked to histamine stimulation. Antihistamines are more effective against extrinsic than intrinsic histamine. This is surprising for, if antihistamines form a chemical bond with the histamine receptor, it is not clear what difference it can make whether the provocative histamine originates close to the effector cells or from remote tissues. It is possible and even likely that the effective concentration of intrinsic histamine greatly exceeds that of the extrinsic histamine—which must be partially inactivated and diluted while it is being carried in the blood stream and distributed to the body tissues. Further, the type of antigen-antibody reaction which is believed to release intrinsic histamine may in fact release a substance other than histamine (the so-called “long-acting substance”); may stimulate the effector cell without a chemical mediator; or disrupt the antihistamine-receptor bond allowing access to histamine. Such explanations are given to account for the diminishing effectiveness of antihistamines in blocking the actions of histamine on smooth muscle, blood vessels and gastric secretion.

### PHARMACOLOGY

(1) *Antihistamine Actions.* Antihistamines are most effective in preventing the increase in capillary permeability (weal forma-

tion) which is a characteristic action of histamine. They do not, however, promote absorption of capillary transudate: the disappearance of local areas of œdema depends on normal osmotic mechanisms. Thus the antihistamines prevent the development of new lesions but do not actively abolish existing ones. This capillary action accounts for their success in the treatment of urticaria, angioneurotic œdema and hay fever. Their ability to prevent contraction of smooth muscle is less marked, and their use in asthma has been correspondingly disappointing. There is evidence that some antihistamines, antazoline and diphenhydramine, for example, are powerful histamine releasers in human lung and may therefore actually promote bronchoconstriction. This may explain, in part, their failure in the treatment of asthma.

Antihistamines do not inhibit the acid-secreting action of histamine.

(2) *Miscellaneous Actions.* Many antihistamines are potent sedative-hypnotics and this is apparent as a side-effect of some preparations in common use. Diphenhydramine and promethazine are particularly liable to produce somnolence. In large or toxic doses the initial phase of cortical depression may be followed by one of hyperexcitability, in which convulsions may occur. It is important, therefore, not to give analeptics during the phase of depression. The sedative property is a useful adjuvant in the treatment of itching dermatoses, but somnolence may be so marked as to prevent the use of certain antihistamines in ambulant patients. Many of the compounds are also mild local anæsthetics and this explains their antipruritic action on topical application.

Certain antihistamines are effective anti-emetic drugs, acting centrally to prevent motion sickness or to diminish the nausea of toxæmic states. Chlorpromazine, cyclizine and meclozine are three of the most efficient anti-emetics. "Dramamine" and "Avomine" are the chlorotheophyllinate derivatives of diphenhydramine and promethazine respectively, and are reputed to possess enhanced anti-emetic properties. They are probably no

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more effective, however, than the parent compounds.

Dryness of the mouth and blurring of vision reveal atropine-like qualities in some of these drugs.

### SIDE-EFFECTS

The incidence and degree of somnolence arising from the administration of antihistamines depend on the particular drug used and on the patient to whom it is given. About 50 per cent of those who receive diphenhydramine experience drowsiness.

Giddiness, tinnitus and confusion sometimes occur. Ingestion of the drugs may lead to anorexia, nausea, vomiting, constipation or diarrhoea. Local application may provoke dermatitis of the sensitisation type. Serious side-effects are rare, but leucopenia and even agranulocytosis have been reported.

**FATE.** Following oral or parenteral administration antihistamines are rapidly absorbed and are active within 15–30 minutes. They are found in maximum concentration in the blood within 1 hour and are almost wholly excreted after 6 hours. As a general rule, therefore, they need to be given four times a day. Promethazine is more slowly eliminated and acts for about 12 hours.

The detailed metabolic fate of antihistamines is largely unknown. Most of the drugs appear in the urine as unidentified degradation products. The main site of degradation is the liver, but the lungs and kidneys take some part in the process.

### USES

Antihistamines are most effective in the treatment of acute allergies which involve the skin and mucous membranes. Thus they are used with great success in urticaria, angioneurotic oedema and hay fever. They can be applied in a penetrating cream to circumscribed areas of urticaria which develop at the site of insect bites and stings. Perennial vasomotor rhinitis is less constantly benefited by antihistamines than its more specific counterpart, hay fever; their action in asthma is altogether unpredictable and disappointing. While antihistamines have a definite role in the treatment of clinical anaphylactic states they do not replace

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adrenaline, which is the only true physiological antihistaminic, and which alone can actively reverse the shock associated with the cardiovascular collapse seen in this condition. Antihistamines control the skin eruptions of serum sickness and drug fever but have little or no direct effect on the constitutional disorder.

Certain antihistamines are specially used for their conspicuous anti-emetic action in such conditions as motion- and radiation-sickness and the vomiting of pregnancy. Others have been tried in Parkinsonism. Their value in the treatment of the common cold is in some doubt, mainly because of the frequent failure to distinguish between allergic rhinitis and true infectious coryza. In so far as they relieve congestion in the nasal mucosa in allergic rhinitis, and thus promote resistance to infection, they may have prophylactic value; but they have no effect on established coryza. Their usefulness in the treatment of Ménière's disease and migraine is not established.

### PREPARATIONS

There is a confusing wealth of almost equipotent antihistamines. Of those mentioned here some are chosen because of their established position in therapeutics and others because of their peculiar anti-emetic property. Trade names are given in brackets.

*Antazoline Hydrochloride* ("Antistin") is prepared as a cream, ointment, injection and tablet or as eye and nose drops. The systemic dose is 100 mg. 2-4 times per day. For topical application it is made up in 0.5 per cent concentration.

*Cyclizine Hydrochloride* ("Marzine") is prepared as a tablet. Dose: 25-50 mg. once per day. It is used solely as an anti-emetic.

*Diphenhydramine Hydrochloride* ("Benadryl") is prepared as capsule, cream, elixir, eyedrops, injection and tablet. Dose: 25-50 mg. 3-4 times per day.

*Meclozine Hydrochloride* ("Ancolan"). It is used as an anti-emetic. Dose: 25-50 mg. once per day.

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*Mepyramine Maleate* ("Anthisan") prepared as a cream, elixir, injection or tablet. Systemic dose is 300–800 mg. per day: given by intravenous or intramuscular injection it is the treatment of choice, combined with adrenaline, in angioneurotic œdema.

*Promethazine Hydrochloride* ("Phenergan") is prepared as a cream, elixir, injection or tablet. Dose: 25–75 mg. per day. It is long-acting, anti-emetic and sedative.

## CHAPTER 10

### DRUGS ACTING MAINLY ON THE HEART

CARDIAC tonics are drugs which improve the functional activity of the failing heart. They act mainly by stimulating the heart muscle but they also have an influence on the nervous mechanism of the heart. The most important members of this class are digitalis, digoxin and ouabain.

#### DIGITALIS LEAF

Digitalis Leaf is the dried, powdered leaf of the common purple foxglove *Digitalis purpurea*.

COMPOSITION. The active principles of digitalis are glycosides:

(1) *Digitoxin* which hydrolyses into the aglucone digitoxigenin and the sugar digitoxose. This is the glycoside mainly responsible for the therapeutic activity of digitalis leaf.

(2) *Gitoxin* which hydrolyses into the aglucone gitoxigenin and digitoxose.

(3) *Gitalin* which hydrolyses into the aglucone gitaligenin and digitoxose.

These glycosides are crystalline, insoluble in water but soluble in organic solvents.

In digitalis leaf digitoxin and gitoxin are combined with one molecule of glucose as precursor glucosides A and B respectively. Gitalin has no corresponding precursor glycoside.

Chemically, the cardiac glycosides consist of a steroid nucleus with an unsaturated lactone ring attached at position C17. This latter ring is essential for cardiac activity.

*Biological Assay of Digitalis.* As different samples of digitalis contain varying amounts of active glycosides, and because there is no easy chemical method of determining total cardiac activity,

digitalis has to be assayed by noting its effect upon animals—the method of biological assay.

There is an internationally agreed Unit of activity and in Great Britain the Reference Standard is maintained by the Medical Research Council. The assay may be carried out using cats, frogs, guinea-pigs or pigeons. In principle, the technique involves comparison of the potency of the unknown powder with that of the standard, the "end point" of the test being death from cardiac arrest in the assay animals. The assayed powder is then adjusted so that 100 mg. contains 1 Unit of activity. This is Prepared Digitalis of the British Pharmacopœia. It is to be noted that in clinical practice dosage is expressed in mg. or G. and not in units.

PHARMACOLOGICAL ACTIONS. *Externally.* The glycosides of digitalis leaf are irritants, if applied to a raw surface or a mucous membrane. This action partly accounts for the nausea and vomiting often produced by large doses of digitalis given by mouth.

*Internally.* The important systemic effects of digitalis are exerted on the cardiovascular system and are best seen in patients with congestive heart failure. It is in this context that the actions will be described and only passing reference will be made to the actions on the healthy heart and the heart in experimental animals.

ACTION ON THE FAILING HUMAN HEART. *On the Heart Muscle.* Digitalis acts directly on the myocardium to increase the force of systolic contraction. The duration of systole is shortened with consequent lengthening of the diastolic phase of the cycle. The work capacity of the heart is increased without a corresponding increase in oxygen consumption so that the mechanical efficiency of heart muscle is increased. The diastolic size of the chambers of the heart tends to decrease. In congestive heart failure these actions result in more complete emptying of the ventricles, a consequent fall in the raised venous pressure, an increase in the cardiac output and an improved blood supply to

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the tissues including the myocardium. This action on cardiac muscle is the most important action of digitalis and can be demonstrated on isolated strips of heart muscle as well as on the intact heart.

*On the Heart Rate.* Digitalis in therapeutic doses tends to reduce the cardiac rate. This action can be demonstrated in animals, in normal human subjects and in patients with congestive heart failure. Decrease in ventricular rate is often most marked in the last group, when heart failure occurs with auricular fibrillation. Three mechanisms are involved in digitalis-induced cardiac slowing.

(1) The tachycardia, which usually accompanies heart failure with sinus rhythm, is generally considered to be a compensatory response. It is brought about reflexly by impulses arising in the walls of the great veins and right auricle—stretched by the increased venous pressure. These reflexes inhibit vagal tone and there is therefore a predominance of sympathetic discharge resulting in tachycardia. By this means an attempt is made to compensate for the low ventricular output. As the tonic effect of digitalis upon the ventricular muscle develops the ventricular output rises and the venous pressure falls. Thus, stretching of the walls of the great veins is reduced and normal vagal inhibition returns. In this way the cause of the tachycardia is removed and the heart rate approaches the normal. In heart failure with sinus rhythm decrease in ventricular rate is mainly brought about by this indirect mechanism. When heart failure occurs with auricular fibrillation, other factors to be described play their part in producing cardiac slowing, but there is no doubt that the improved myocardial action leads indirectly to a reduced ventricular rate. In auricular fibrillation without heart failure, the ventricular rate at rest is commonly the optimum.

(2) *Action on Conducting System.* Therapeutic doses of digitalis cause slower conduction through the junctional tissues between auricle and ventricle, and increase the effective refractory period of junctional tissue. This action is mainly a direct effect on the junctional tissue, but is partly brought about by the vagus action



(see below) which also impairs conduction of the impulse between auricle and ventricle. In the presence of sinus rhythm, no reduction in ventricular rate will result from these actions on the Bundle of His, although auriculoventricular delay may be demonstrated by an increase in the P-R interval in the electrocardiogram. In the presence of auricular fibrillation, however, impulses at the rate of about 500 per minute bombard the junctional tissues; many are intercepted or "blocked" and do not reach the ventricle, but the numerous impulses that escape this blocking action produce rapid and irregular ventricular beating—especially if there is heart failure. When digitalis is given in these circumstances the depression of auriculoventricular conduction produced will result in further blockade of conduction with consequent fall in the ventricular rate. Toxic doses of digitalis may result in higher degrees of heart block to the point of complete auriculoventricular dissociation.

(3) *Actions on the Vagus.* Digitalis produces an increase in vagal tone with consequent cardiac slowing, which can be abolished by atropine. The action is believed to be a reflex one consequent upon sensitisation of the carotid sinus and is not caused by a direct action on the vagal centres and terminations. In heart failure, the mechanisms already mentioned, (1) and (2), are more important in determining cardiac slowing than the effect of digitalis on the vagus.

*Cardiac Output, Heart Size, Venous Pressure, Blood Pressure.* In heart failure the cardiac output rises as a result of digitalis therapy. The increased venous pressure falls towards normal and the diastolic size of the heart decreases. The effects are in consequence of the direct myocardial action of digitalis. In the normal person the cardiac output may fall slightly and this is probably due to the fact that the heart is decreased below its optimal size by the direct action of the drug on the myocardium. In the normal heart the venous pressure is not significantly affected. No constant effect on the blood pressure is observed in patients with heart failure under treatment with digitalis and usually little change occurs. In severe heart failure the blood pressure may rise as

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improvement occurs in the force of systolic contraction of the ventricle.

*Diuretic Action.* In patients with congestive heart failure and œdema a marked diuresis may result from treatment with digitalis. This effect follows improved renal blood flow consequent upon the increased cardiac output and the fall in venous pressure which allows the œdema fluid to return to the blood. Thus, the diuretic action is secondary to the effects of the drug on the heart: digitalis has no important direct actions upon the kidney. Diuresis does not occur in the normal subject, nor when œdema is due to causes other than heart failure. When the failing heart does not respond to the drug, diuresis does not occur.

*Effect of Digitalis on the Electrocardiogram.* The earliest effect of the drug is upon the RS-T segment and 'T' wave. The RS-T segment sags below the base line and the 'T' wave may become isoelectric or inverted. This change is due to acceleration of the repolarisation process which begins before depolarisation is complete.

The Q-'I' interval is shortened—a reflection of the shorter duration of ventricular systole. With larger doses the P-R interval may be prolonged and this is due to the vagal action of the drug and to its direct depression of the conducting tissue. The U wave sometimes becomes prominent. Higher grades of A-V block and various arrhythmias (see below) do occur with digitalis overdosage and the electrocardiogram is then invaluable for their accurate interpretation.

*Effect on the Refractory Period, Excitability and Conduction Velocity.* The action of digitalis on these properties of heart muscle is complex and the auricle, conduction tissue and ventricle respond in different ways.

*Auricle.* In the normal heart the refractory time of the auricle is shortened and the conduction velocity is increased. Both these effects are mediated reflexly via the vagus nerve. In the experimentally denervated auricle, however, the action of digitalis is to

lengthen the refractory time and slow the rate of conduction.

In naturally occurring auricular fibrillation in man the usual effect is to increase the "f" wave rate and to perpetuate the abnormal rhythm. Presumably the vagal effects of the drug predominate over the direct myogenic action.

In auricular flutter treatment with digitalis often leads to a change to auricular fibrillation because of the increase in velocity of conduction. If digitalis therapy be discontinued when this change occurs, a reversion to sinus rhythm will occur in a proportion of cases. In the remainder, auricular fibrillation persists or auricular flutter returns as the effects of the drug pass off. Established auricular fibrillation is rarely if ever converted to sinus rhythm by digitalis.

*Conduction Tissue.* The refractory period of this tissue is lengthened by digitalis and the rate of conduction is slowed. The importance of these effects in slowing the ventricular rate in auricular fibrillation has already been considered (p. 289).

*Ventricular Muscle.* The refractory time of ventricular muscle is shortened by digitalis and there is an increased tendency to automatic beating and ventricular ectopic rhythm. The intraventricular conduction time is little changed even with large doses of digitalis.

*Mode of Action at Cellular Level.* The details of the mode of action of digitalis on failing heart muscle have not yet been elucidated. The available evidence suggests that the glycoside corrects the impaired energy utilisation which is known to occur in cardiac failure. Alteration of the permeability of the cell membrane to potassium ions plays an important part in this action.

**DIGITALIS INTOXICATION.** (i) *Early Toxic Effects.* Because of the slow excretion of digitalis, cumulation in the body with production of toxic effects readily occurs. Further, as the aim of therapy is to maintain the full therapeutic effect short of poisoning, the early symptoms of intoxication are important. These are most commonly a distaste for food or even slight nausea. If treatment be continued at the same dosage level retching and vomiting will occur. Abdominal discomfort and occasionally diarrhoea may accompany these symptoms. Whilst digitalisation with large doses

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by mouth produces nausea and vomiting from irritation of the gastric mucosa, the clinically important gastro-intestinal symptoms referred to above are of *central* origin. They are due to stimulation of the central emetic mechanism in the medulla, probably the chemoreceptor trigger zone on its surface. In some persons headache is a prominent symptom. It is inconstant, but may precede the gastro-intestinal symptoms.

(ii) *Later Toxic Effects—mainly upon the Heart.* The most frequent effect of digitalis overdosage upon the heart is the occurrence of extrasystoles, usually ventricular in origin. These may occur regularly after each conducted beat, giving rise to the well-known digitalis coupling—*pulsus bigeminus*. The appearance of this irregularity in a patient under treatment with digitalis is certain evidence of overdosage and calls for temporary discontinuation of therapy.

Excessive slowing of the ventricular rate due to high grade A-V block may also occur. It is customary to regard a ventricular rate of under 60 beats per minute as evidence of digitalis overdosage, but in some patients optimum therapeutic effects accompany ventricular rates of this order without other signs of poisoning.

*Arrhythmia.* Almost every known type of arrhythmia can occur in digitalis poisoning and is most likely to be seen in patients with advanced heart disease. Particularly ominous is the occurrence of ventricular tachycardia, which may be a prelude to fatal ventricular fibrillation. This is the commonest cause of death from digitalis poisoning. Auricular tachycardia with or without a variable degree of A-V block also occurs as a manifestation of digitalis overdosage.

It has recently been recognised that electrolyte imbalance, especially potassium depletion, sensitises the heart to the action of digitalis and increases the tendency to ectopic rhythm. Potassium depletion also accounts for the sudden appearance of signs of digitalis poisoning following a massive diuresis induced with organic mercurial or other diuretics. Formerly this was attributed to the mobilisation into the blood stream of digitalis glycoside from oedema fluid, under the influence of the diuretic.

The appearance of unexpected tachycardia in a patient under

treatment with digitalis demands immediate cessation of digitalis therapy. Electrocardiograms are essential to determine accurately the rhythm change. The plasma concentrations of electrolytes should be determined and appropriate replacement therapy instituted if this is indicated. If the ECG shows auricular tachycardia with A-V block, potassium depletion can be assumed and potassium salts should be administered by mouth or by slow intravenous infusion (drip technique). The use of quinidine and procainamide in the treatment of digitalis-induced tachycardia is discussed on p. 308. It must be emphasised that arrhythmia may be the first sign of digitalis overdosage.

(iii) *Miscellaneous Toxic Effects.* Other disturbances which occur—though infrequently—in digitalis poisoning include visual disturbances with white, red or blue vision and transient amblyopia. Neurological symptoms including facial pain, peripheral neuritis and mental confusion are sometimes seen. Confusion most often occurs in elderly patients and it is often difficult to distinguish the part played by digitalis from the effects of cerebrovascular disease and water and salt depletion.

In summary, the important early features indicating that therapeutic doses have been exceeded are malaise and loss of appetite, nausea, vomiting and sometimes headache. Coupled beats are certain evidence of overdosage. Rarely, but especially in patients depleted of electrolyte, arrhythmia may be the first sign of serious intoxication.

PREPARATIONS OF DIGITALIS AND ITS GLYCOSIDES. Digitalis is prepared for use as Tablets each containing 30 mg. or 60 mg. of Prepared Digitalis—the leaves of *Digitalis purpurea*, the common foxglove, which have been dried, powdered and standardised. A tincture is also available, 1 ml. being equivalent in potency to 100 mg. of Prepared Digitalis. The tincture possesses no advantages over the tablet: on the contrary it slowly loses its potency on keeping and it is now seldom used. These preparations are administered by mouth.

*Digoxin.* This glycoside is prepared from a different variety of digitalis—*Digitalis lanata*. It is a chemically pure substance and biological assay is therefore unnecessary. It is available as tablets

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each containing 0.25 mg. for oral use and as Digoxin Injection containing 0.5 mg. in 1 ml. of 70 per cent alcohol. The latter preparation is intended for intravenous injection and is diluted to 10 ml. with normal saline before use.

**Ouabain.** Ouabain is a crystalline glycoside obtained from the seeds of *Strophanthus gratus*. It is soluble in 100 parts of water and is prepared for use in ampoules each containing 0.25 mg. of ouabain in 1 ml. It is administered intravenously.

In addition to the glycosides listed above, others are available for clinical use. They include Digitoxin, Nativelle's Digitaline and Lanatoside C. These preparations are effective but generally they have no special advantages and will not be considered in detail. Rarely, a patient may be nauseated even by small doses of the standard remedies, apparently because of the irritant effect of the glycoside upon the gastric mucosa. An alternative remedy—such as one of those mentioned above—may then prove useful. In Lily of the Valley, Squill and many other plants there are glycosides which have pharmacological actions similar to those of digitalis, but they are not in general clinical use.

**Dosage.** In the treatment of heart failure with digitalis the aim is to administer sufficient of the drug to produce optimum benefit to the patient without incurring the risk of intoxication, and to maintain this effect for as long as may be necessary. Usually this means for the rest of the patient's life.

It is desirable to bring the patient fully under the influence of digitalis as quickly as possible without serious risk of poisoning but there is seldom extreme urgency. Clinical experience has shown that about 1.5 G. to 2 G. of digitalis given in divided doses over a period of 3–4 days will suffice to produce maximum benefit in most patients. Because of the slow exponential renal clearance of digitalis to a maximum corresponding to an oral dose of 0.2 G. daily, the full effects of the drug can be maintained by giving a daily dose sufficient to replace the daily loss from the body—commonly about 0.12 G. daily. The drug is given at 6–8-hourly intervals initially to allow time for the full effect of each dose to be produced and maintenance doses may be given at 12-hourly intervals.

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A satisfactory regimen is to give 0.12 G. at 6-hourly intervals until full therapeutic benefit is obtained, and thereafter to continue treatment with 0.06 G. twice daily. A careful watch must be maintained for signs of poisoning and medication temporarily discontinued should these occur. It must be stressed that the doses mentioned above represent average doses and there are considerable individual variations. The drug cannot be given by rule of thumb methods and the proper maintenance dose must be found by careful observation of the patient. Elderly patients often require less of the drug than younger persons while children may require proportionately more. It is not satisfactory to attempt to administer the drug on a strict body weight basis, e.g. 0.1 G. per 10 lb. of body weight as the digitalising dose, because of the variations which occur from person to person.

It should be remembered that it is possible to produce the full effects of digitalis by giving say 0.06 G. thrice daily, but in this case about 14 days will elapse before the full benefits are achieved.

Digoxin may also be given orally in a similar manner to digitalis. The average dose to produce full digitalisation is 2-4 mg. given in divided doses. 0.5 mg. may be given every 6 hours and full therapeutic effects may be expected in 2-3 days. Thereafter a maintenance dose of 0.25-0.75 mg. daily depending upon the individual patient will be required. In urgent cases full digitalisation may be accomplished in 12-24 hours by giving an initial dose of 1 mg. of digoxin followed by 0.5 mg. 6-hourly but a careful watch must be kept for signs of intoxication.

In cases of extreme urgency digoxin or ouabain may be used intravenously, and this route is also employed if vomiting or coma make oral administration impossible. 0.5-1 mg. of digoxin or 0.25-0.5 mg. ouabain should be administered slowly intravenously. Subsequent dosage is adjusted depending upon the response of the patient, and oral therapy instituted as soon as possible.

Initial large doses of cardiac glycosides should not be given to patients who have received digitalis during the preceding 10 days. Intravenous administration is particularly dangerous in these circumstances.

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**Absorption, Fate and Excretion.** Information about the absorption, fate and excretion of cardiac glycosides is incomplete. The main facts are as follows:

When digitalis is given, by mouth only about 20 per cent of its contained glycosides is absorbed from the upper intestine and absorption takes about 2 hours. However, pure digitoxin is almost completely absorbed in this period of time. About one-half of the administered dose of digoxin is absorbed, but ouabain is so irregularly and poorly absorbed that oral administration of this drug is not recommended. Absorption from subcutaneous tissue and muscle is slow and irregular, and as such injections cause local irritation and pain these routes of administration are not used.

**Fate.** Digitoxin circulates partly bound to plasma albumin and its action on the heart develops slowly. It begins after about two hours but is not maximal for 4-12 hours even after intravenous administration. The heart does not selectively concentrate digitoxin but appears to contain more digitoxin metabolites than does other tissue. The fate of digitoxin is unknown but the liver appears to be the site of degradation of digitoxin not excreted unchanged in the urine. Digoxin is bound to plasma protein minimally and this may explain its more rapid action on the heart.

**Excretion.** The glycosides of digitalis are eliminated very slowly by the kidney as degradation products. About 1/19 of the total body content of the glycosides of *Digitalis purpurea* is eliminated daily by the kidney to a maximum corresponding to an oral dose of about 0.2 G. daily. Following a single dose of digitoxin intravenously more rapid excretion occurs during the first 24-48 hours, but degradation products can still be detected for upwards of 6 weeks. Only about 10 per cent of the dose is excreted as unchanged digitoxin. The very slow excretion of digitoxin accounts for the ease with which cumulation and toxic effects may occur after repeated dosage, and for the fact that the effects of digitoxin may persist for 2-3 weeks after administration has been discontinued. Digoxin is eliminated much more rapidly and its effects have largely disappeared in about 6 days.



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Ouabain is excreted even more quickly and after therapy is discontinued the drug is effectively eliminated in about 3 days.

*In summary*, digitalis requires 6–12 hours to develop the full action of a given dose, 2–3 days for regression of its action and 2–3 weeks before effective elimination is complete. Digoxin takes 2–5 hours to develop its full effect. The action begins to pass off in about 12 hours and elimination is complete in about 6 days.

Ouabain begins to act in a few minutes after intravenous injection; its full effect is seen in 1–2 hours. Elimination is complete in 3 days.

### THERAPEUTIC USES

It must be emphasised that the presence of organic heart disease is not by itself an indication for digitalis therapy. If the circulation is efficient treatment with digitalis is unnecessary. The effects of digitalis must be carefully watched because patients exhibit differences in reaction to the drug, and it is important that the dosage be so adjusted as to produce maximal benefit to the circulatory system in each case.

**HEART FAILURE.** This syndrome constitutes the prime indication for the use of digitalis. It matters little whether the underlying heart disease be valvular, hypertensive or ischaemic, nor is it important whether the rhythm is sinus rhythm or that of auricular fibrillation. Left ventricular failure responds as well as congestive heart failure.

It is true that in chronic pulmonary heart failure and in such conditions as severe anaemia, beri-beri, and generalised Paget's disease of bone, which produce syndromes resembling heart failure, the response is often disappointing compared with the results seen, for example, in cardiac failure associated with mitral stenosis with auricular fibrillation, but digitalis should be tried if it is thought that true heart failure is present.

Successful treatment with digitalis results in increased ventricular output, a fall in the elevated central venous pressure, recession of the enlarged liver, diminished pulmonary congestion,

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lessening of peripheral œdema and diuresis. Slowing of the ventricular rate is the rule, but on occasion pronounced benefit may be obtained with little cardiac slowing. Reduction in the ventricular rate is greatest in cases of auricular fibrillation, but even when this rhythm is present the ventricular rate seldom falls to within the normal range until signs of heart failure have disappeared.

**CARDIAC ARRHYTHMIAS.** *Auricular Fibrillation.* When this arrhythmia occurs without heart failure, the ventricular rate is often well controlled and the use of digitalis is unnecessary. However, some patients experience unpleasant palpitation on effort due to the increased ventricular rate. In these circumstances digitalis therapy may prevent this occurrence. As already indicated the drug does not restore sinus rhythm and indeed tends to perpetuate the abnormal rhythm.

When auricular fibrillation is caused by thyrotoxicosis, digitalis should be given and appropriate measures to render the patient euthyroid are urgently indicated. In these cases control of the heart rate and relief of the symptoms of heart failure will not be obtained until the thyrotoxic state has been treated (p. 361).

*Auricular Flutter.* Digitalis is given in the usual manner when heart failure is present. It is, however, sometimes possible to convert this arrhythmia to auricular fibrillation by the use of digitalis. If the drug is then discontinued, normal sinus rhythm will be restored in about one-third of such cases. In the remainder auricular fibrillation will persist or the rhythm will revert to auricular flutter. Digitalis may then be used to control the ventricular rate or if indicated quinidine may be used to restore sinus rhythm.

*Paroxysmal Tachycardia.* In supraventricular tachycardia digitalis is indicated if signs of incipient heart failure are present. It is best to give digoxin or ouabain to produce rapid digitalisation. The paroxysm may thus be quickly terminated. These arrhythmias also respond to other measures such as carotid sinus pressure and also quinidine therapy—which should be used if there is no evidence of heart failure. In the supraventricular paroxysmal tachycardias of infancy digoxin 0.1 mg. intravenously is the

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treatment of choice. Digitalis should not be used in tachycardia of ventricular origin except in very special circumstances.

**CONDITIONS MODIFYING THE USE OF DIGITALIS.** Digitalis should be used with care when recent myocardial infarction is the cause of heart failure. Rapid digitalisation is unwise as fatal ventricular tachycardia may be precipitated. Slow digitalisation and the other measures of value in heart failure are usually preferable. However, recent evidence suggests that in the shock syndrome of severe myocardial infarction fractional doses of digoxin or ouabain given intravenously may be of value. In toxic myocarditis, e.g. due to diphtheria, digitalis is contra-indicated but in acute rheumatic carditis with heart failure it should be given in the normal manner.

**OTHER DRUGS.** Mention has already been made of the possible sensitisation of heart muscle to digitalis by decreased concentrations of potassium. Increase in the concentration of calcium in the body fluids in relation to digitalis therapy is referred to on p. 409.

The use of quinidine and procainamide in relation to digitalis medication is considered on p. 308.

## QUINIDINE

Quinidine is the dextrorotatory isomer of quinine and occurs naturally in cinchona bark. It possesses all the pharmacological properties of quinine but is only used in therapeutics in the treatment of disorders of cardiac rhythm, as its action on heart muscle is more specific and effective than that of quinine. Only its effects upon heart muscle will be described here, and the reader is referred to Chapter 16 for an account of the other actions of the cinchona alkaloids.

*Actions on Cardiac Muscle.* The essential action of quinidine is that it depresses myocardial excitability and rhythmicity. Thus in excessive doses it poisons the heart muscle and causes cardiac standstill. More specifically, quinidine prolongs the effective refractory period of both auricular and ventricular

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muscle, by as much as 50–100 per cent. This is probably its most important action and the one which mainly determines its therapeutic usefulness in auricular fibrillation and ventricular tachycardia.

Conduction of the impulse in the auricle, junctional tissues and ventricular muscle is slowed by quinidine and these effects can readily be demonstrated electrocardiographically. This action is mediated in part by the antivaagal action of the drug (see below).

In large doses quinidine depresses the contractility of heart muscle and produces peripheral vasodilatation from a direct relaxant action upon arteriolar muscle. These two actions may produce an alarming fall in blood pressure in susceptible individuals or if the drug is given intravenously. Quinidine also exerts an atropine-like action upon the heart and this accounts for the sinus tachycardia which is often seen when the drug is successful in restoring sinus rhythm in the patient with arrhythmia. This action also helps to increase the effective refractory time of auricular muscle and to slow the speed of conduction of the accession wave through the auricles. On the A-V node, however, the anticholinergic action of the drug opposes its direct depressant effect.

*Toxic Effects and Side-effects.* Quinidine in common with quinine may give rise to the symptoms and signs collectively known as "cinchonism" which is fully described in the section dealing with quinine. It should be remembered that there is a remarkable difference in susceptibility to the action of the drug from person to person: a dose of 0.2 G. of quinidine sulphate may occasionally produce distinct side-effects such as ringing in the ears, vertigo or gastro-intestinal symptoms; in another patient as much as 4 G. may be given daily without the appearance of such symptoms. There is a similar wide variation in the amounts of the drug required to produce the desired effect upon the heart leading to restoration of normal rhythm, and serious side-effects may appear before the abnormal rhythm has been abolished. Conversely, in many patients the ectopic rhythm may be controlled with a dose of the drug which does not produce any of the features of cinchonism. Fortunately severe cinchonism is relatively infrequent with the doses which are commonly effective

in restoring sinus rhythm or preventing the recurrence of the abnormal rhythm.

(i) *Idiosyncrasy*. Idiosyncrasy to quinidine is rare. The most important feature of this is the occurrence of thrombocytopenic purpura which, on rare occasions, has proved fatal. Its onset bears no relation to the dose or duration of therapy and it is likely to recur if the drug is again administered after the patient has recovered. Asthma and skin manifestations of idiosyncrasy are also seen occasionally.

(ii) *Depression of Myocardium*. It is not surprising that a drug with a variety of depressant actions such as have been described should sometimes give rise to dangerous cardiac toxic effects. These include prolongation of A-V conduction with varying degrees of heart block, intraventricular block and rarely fatal cardiac asystole or ventricular fibrillation. Extrasystoles and ventricular tachycardia have also occurred as manifestations of quinidine toxicity. All these effects may be seen in the electrocardiogram, and it is desirable that electrocardiographic facilities be available for patients who are being treated with quinidine in order to detect toxic manifestations of the drug as well as to confirm the restoration of normal rhythm.

(iii) *Embolism*. In patients with auricular fibrillation thrombi may form in the auricular appendages and if quinidine therapy restores sinus rhythm in such patients the resultant complete contraction of the auricles (as distinct from fibrillation) may dislodge a thrombus and cause occlusion of a major artery with serious effects. The current view, however, is that this danger of quinidine treatment has been exaggerated; it is doubtful if the incidence of emboli is greater when quinidine is employed, than when the drug is withheld.

*Absorption, Fate and Excretion*. Quinidine is rapidly absorbed from the upper gastro-intestinal tract and less than 5 per cent of the ingested dose appears in the faeces. The drug circulates largely bound to plasma protein and is not specially concentrated in heart muscle. Peak levels are reached in the plasma about three hours after a single dose; the level has markedly fallen by 6 hours and none can be detected after 24 hours. About 5 per cent of the drug is excreted unchanged in the urine, another 5 per cent

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appears as metabolites, but the bulk of the drug is metabolised in some way not understood. There is some evidence that the metabolism of quinidine in patients with congestive heart failure is slower than in normal persons.

*Preparations and Dosage.* The official preparation of Quinidine is the Sulphate with a single dose of 0.2–0.3 G. The drug is dispensed in tablets each containing 0.2 G. or 0.3 G. Quinidine sulphate is relatively insoluble (1 in 90 in water) and it is therefore unsuitable for parenteral injection. More soluble salts, e.g. the lactate and gluconate, have been prepared for intramuscular and intravenous injection but they are not generally available. On the rare occasions when the parenteral use of the drug might be deemed necessary, a soluble salt of *quinine* can be used. However, procainamide (see below) is to be preferred in this eventuality.

*Dosage.* Many different schemes of quinidine dosage have been proposed, depending upon the type of abnormal rhythm under treatment and the urgency with which its abolition is considered necessary. For example, in a patient with ventricular tachycardia large doses of quinidine at short intervals will often be desirable in order to secure restoration of sinus rhythm as quickly as possible. On the other hand in less urgent cases the frequency of administration may be reduced with less hazard to the patient, but it will take longer for adequate plasma levels to be attained. As already indicated the amount of quinidine required varies greatly from patient to patient and there is no means of predicting how much will be needed. The dose required to prevent recurrence of the abnormal rhythm after sinus rhythm has been restored may be smaller than the initial dose, but it is not infrequently larger, and the correct dosage for a particular patient can be determined only by trial and error. It is customary to administer initially a "test dose" in order to detect hypersensitiveness to the drug, but the first dose given may be considered to be the "test dose".

In non-urgent cases 0.2 G. quinidine sulphate may be given at 4-hourly intervals omitting the dose at night, i.e. five times daily. The patient should be examined before each dose and the rhythm noted.

Repeated electrocardiographic examination is often helpful and

sometimes essential in controlling therapy. Maximum stable blood levels will be reached in such a dosage scheme in 3-4 days, and if normal rhythm has not been restored by this time the dose should be raised by increments of 0.2 G. every fourth day until sinus rhythm is restored or toxic effects make further therapy impossible. If maintenance therapy is required after successful restoration of sinus rhythm, 6- to 8-hourly dosage is often adequate. In urgent cases, for example ventricular tachycardia, 0.4 G. should be given every 2 hours until the paroxysm is abolished.

**INDICATIONS FOR USE.** Quinidine is used in the treatment of various cardiac arrhythmias including the following: auricular fibrillation, auricular flutter, auricular tachycardia, nodal tachycardia, ventricular tachycardia and premature systoles. The drug is also used to prevent the occurrence of these abnormal rhythms.

*Auricular Fibrillation.* The indications for, and contra-indications to, the use of quinidine in established auricular fibrillation are beyond the scope of this book. Generally, heart failure should be under control and the patient digitalised before quinidine therapy is instituted. The dosage schedule indicated for non-urgent cases is satisfactory. Maintenance therapy may or may not be required according to circumstances.

The paroxysmal form of auricular fibrillation will often respond to quinidine 0.4 G. given every 2 hours until sinus rhythm is restored. To prevent recurrent attacks up to 2 G. daily may be needed, sometimes even larger amounts.

*Auricular Flutter.* The use of digitalis in this disorder has already been noted. If digitalis is unsuccessful, quinidine therapy may be tried while a maintenance dose of digitalis is continued. Dosage along the lines indicated for auricular fibrillation should be used, but it is more difficult to secure normal rhythm in this arrhythmia than in auricular fibrillation. It is wise to maintain digitalis therapy because otherwise, as the rate of the auricular wave decreases under the influence of quinidine, the Bundle of His may again transmit *all* the auricular impulses—at rates of over 200 per minute. Life may be endangered if this happens. The block imposed by digitalis upon the junctional tissues tends to prevent this occurrence.

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*Auricular and nodal tachycardia* may be treated with quinidine if measures designed to produce vagal stimulation fail to terminate the paroxysm, and quinidine may also be used to prevent recurrences in patients subject to frequent attacks of this disordered rhythm.

*Ventricular Tachycardia.* This usually serious rhythm change calls for vigorous treatment with quinidine in doses of 0.4 G. every two hours. Electrocardiographic control is necessary. If quinidine intolerance develops before the rhythm has returned to normal other measures, for example procainamide, should be used. In digitalis-induced ventricular tachycardia quinidine should probably not be given.

*Premature Beats.* Quinidine can be used to suppress extrasystolic beats which are frequent and troublesome. A relatively small dose often suffices. Following myocardial infarction it should be used if frequent ventricular extrasystoles appear, as these may be a prelude to the onset of ventricular tachycardia and fatal ventricular fibrillation. Its routine use in myocardial infarction to prevent ectopic beats is not advocated, nor can it be recommended as routine medication to prevent mechanically induced arrhythmia at operation or cardiac catheterisation.

### PROCAINAMIDE

Procainamide has been introduced in recent years as an anti-arrhythmia agent, following the observation that procaine possessed a quinidine-like action on heart muscle. Chemically, procainamide differs from procaine only in the substitution of an NH group in the former compound for an oxygen linkage in procaine. Qualitatively its effects on heart muscle are similar to those of quinidine.

*Actions on Cardiac Muscle.* Procainamide, like quinidine, prolongs the refractory time of heart muscle, but this effect is much more marked in auricular muscle than in the ventricle. The excitability and rhythmicity are also depressed and the rate of conduction is decreased in the auricle, ventricle and junctional tissues especially in the A-V node. Procainamide does not affect the contractility of the heart and thus its action differs from that of quinidine. Again, procainamide possesses anticholinergic



properties, so that sinus tachycardia may result when normal rhythm has been restored. These actions are reflected in the electrocardiogram and a lengthened P-R interval, widening of the QRS complex and Q-T intervals, and T wave changes may be seen after therapeutic doses in man.

*Other Actions.* Like procaine, the amide also acts as a local anæsthetic and it produces vasodilatation by a direct action on arteriolar muscle, but this latter effect is usually seen only if large doses are given intravenously. The central nervous system actions of procainamide are less marked than those of the parent substance, but mental confusion and hallucinations have been described in man. Finally, procainamide is a weak autonomic ganglionic blocking agent.

*Toxic Effects and Side-effects. Cardiovascular system.* As in the case of quinidine, procainamide can cause serious cardiac toxicity because of its depressant actions upon the heart muscle and the junctional tissues. Accordingly heart block, intraventricular block and on occasion cardiac arrest may occur. Ectopic ventricular rhythms have also occurred in patients with advanced heart disease and have sometimes proved fatal. Serious toxic effects are more likely to occur when the drug is administered intravenously and this route of administration should be used only in serious emergency; and the injection should be made slowly. Hypotension, which may be severe, also occurs when the intravenous route of administration is used, especially if ventricular tachycardia is present.

Side-effects may also occur in *other systems*. By mouth the drug may give rise to nausea, vomiting and diarrhœa, particularly if the daily dose exceeds 5 G. A continuous bitter taste may be troublesome. Mental depression and hallucinations have been reported. Hypersensitivity reactions may also develop with fever, joint pains, skin eruptions and agranulocytosis.

*Absorption, Fate and Excretion.* Procainamide is rapidly and completely absorbed from the upper intestinal tract and peak levels are reached in the blood within 2 hours after oral administration or after 1 hour when the drug is given intramuscularly. The drug is concentrated in the tissues and the plasma levels

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decline at about 15 per cent per hour. Six per cent of the ingested dose can be recovered unchanged in the urine and a further 10 per cent is excreted as *para*-aminobenzoic acid either free or conjugated. If the drug is given at 6-hourly intervals stable plasma levels occur in 24-48 hours.

*Dosage and Administration.* Procainamide Hydrochloride is available as Tablets each containing 250 mg. for oral use and as a Solution for Injection containing 100 mg. per ml. This is supplied in 10 ml. phials and is suitable for intramuscular or intravenous injection. The drug should usually be given by mouth in a dose of 0.5-1 G. 4-hourly. If no effect is produced after 48 hours the dose may be increased, as stable plasma levels are reached by this time. Maintenance doses are usually given at 6-hourly intervals. The intramuscular route can be used if the oral route is not feasible, and a dosage of 0.5-1 G. at 6-hourly intervals is suitable. The intravenous route should only be used if the arrhythmia is considered to be endangering life or if the other routes have failed. The solution should be well diluted, and administered at a rate not exceeding 50 mg. per minute. A careful watch should be kept upon the blood pressure, and cardiographic control is essential. Solutions of a suitable sympathomimetic amine should be at hand to counteract severe hypotension.

**THERAPEUTIC USES.** Procainamide is used to abolish or to prevent certain cardiac arrhythmias. The best results are obtained in ventricular extrasystoles, ventricular tachycardia, nodal tachycardia and auricular fibrillation of recent onset. In other arrhythmias, for example auricular flutter or established auricular fibrillation, the drug is not generally useful. It can be usefully employed in myocardial infarction as a prophylactic measure in the prevention of ventricular arrhythmia. It is also widely used to prevent arrhythmia mechanically induced at cardiac catheterisation or during cardiac surgery, but its value in this respect is not wholly established.

Procainamide has also been used in conjunction with a ganglionic blocking agent to produce "controlled hypotension" in certain surgical procedures.

*Digitalis in relation to Quinidine and Procainamide Therapy.* There is no doubt that both quinidine and procainamide can abolish digitalis-induced ventricular extrasystoles and ventricular tachycardia, and there is also strong evidence that in the presence of the latter arrhythmia, both quinidine and procainamide are more likely to induce fatal cardiac asystole or ventricular fibrillation. Each case must be judged on its own merits and the possible dangers of administration of quinidine or procainamide must be balanced against the possible benefit to be derived from reversion to normal rhythm. As already mentioned therapeutic doses of digitalis are desirable before attempts are made to secure reversion to sinus rhythm in patients with established auricular fibrillation and auricular flutter.

Certain other drugs are sometimes used in the treatment of cardiac arrhythmias. These include mechlorin, papaverine, magnesium sulphate and phenylephrine. They are mentioned in other sections of the book.

## VASODILATORS AND HYPOTENSIVE AGENTS

The following drugs, whose main action leads to vasodilatation and lowering of blood pressure, are discussed in this section—nitrites, khellin, veratrum alkaloids, rauwolfia and hydrallazine. Many other remedies which cause vasodilatation and hypotension are considered elsewhere in the book; they include adrenergic blocking agents and ganglionic blocking agents.

### THE NITRITES

The term "nitrite" includes inorganic and organic nitrites and certain organic nitrates which exhibit the "nitrite" type of action in the body. Inorganic nitrates do not possess this type of pharmacological action.

The official compound is Glyceryl Trinitrate. Amyl nitrite, octyl nitrite and pentaerythritol tetranitrate (PETN) are also used therapeutically, while sodium nitrite has a unique use in the treatment of cyanide poisoning. Other nitrites are seldom used in modern therapeutics.

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**PHARMACOLOGICAL ACTIONS.** All the nitrites have essentially the same type of pharmacological action but they differ in their duration and intensity of action. The basic action is to relax smooth muscle. This effect is a direct one on the smooth muscle cell and is independent of its nerve supply. Arterioles, capillaries and venules are particularly affected, but plain muscle in larger arteries and other structures is also affected to a lesser degree. The relaxed muscle is still capable of contracting in response to direct stimulation or by excitation of its motor nerve supply.

*Cardiovascular System.* The most important action of nitrite is to dilate arterioles, capillaries and venules and to a lesser extent arteries and veins. The dilatation is widespread, involving in some degree all the vascular beds of the body, though the skin vessels are prominently dilated by the quick-acting nitrites only, and the blush area is mainly involved. The pulmonary vessels are minimally affected. The coronary vessels are consistently dilated with an increase in coronary blood flow.

This action upon blood vessels results in a fall in blood pressure, the speed and degree of fall depending upon the preparation of nitrite used. The systolic pressure falls more than the diastolic and with therapeutic doses of glyceryl trinitrate used in the treatment of angina pectoris the fall in blood pressure is usually slight. Large doses of nitrite may lead to syncope in the upright posture due to pooling of blood in capillaries and venules with diminished venous return to the heart. Throbbing in the head and neck, and flushing of the skin of the face, neck and upper trunk are also commonly produced by quick-acting nitrites due to vasodilatation. The healthy myocardium is not directly affected by nitrite. The tachycardia occurring after quick-acting nitrites is a carotid sinus mediated reflex, in response to the falling blood pressure, and is most marked after the inhalation of amyl nitrite. Therapeutic doses of nitroglycerin do not usually cause significant changes in the cardiac output, but the peripheral vascular resistance is lowered with a reduction in left ventricular work. The pulmonary vascular resistance and right ventricular work remain unchanged. After inhalation of amyl nitrite, however, there is a conspicuous rise in the cardiac output which is short-lived. The ECG is not

directly affected by nitrite, though changes due to cardiac ischæmia may regress when anginal pain is relieved by nitrite.

*Mode of Action of Nitrite in Relief of Cardiac Pain.* Angina pectoris is produced by relative myocardial anoxia, though it is not certain whether the anoxia itself or excessive metabolite production by the anoxic myocardium stimulates the afferent pain receptors. Quick-acting nitrites rapidly relieve anginal pain and have been shown to reverse the abnormal metabolic changes of ischæmic cardiac muscle. Whether this is a direct effect of nitrite or whether it is due to relief of anoxia consequent upon the increased coronary blood flow is not known.

*Non-vascular Smooth Muscle.* Nitrite relaxes the smooth muscle of the bronchi, the biliary tract, gastro-intestinal tract and genito-urinary tract. The effect is most marked with amyl nitrite. A more prolonged, but less intense action is obtained with glyceryl trinitrate, while the longer-acting nitrites have little effect.

*Nervous System.* Nitrite has no direct effect upon the nervous system in man. The giddiness which may occur after large doses of nitrite is due to cerebral anoxia as already noted and transient visual disturbance may also be due to this effect.

The rate and depth of breathing are increased by nitrite due to a respiratory reflex mediated through the carotid body.

*Toxic Effects.* Reference has been made to the throbbing headache, facial flushing and faintness induced by quick-acting nitrites. With large doses of nitrite or with therapeutic doses in susceptible persons syncope may occur. This can usually be relieved by lying down, by the head-low position, and in general by procedures which facilitate venous return. Vasoconstrictors such as sympathomimetic amines are not effective and may make matters worse, as in severe nitrite-induced shock reflex arteriolar vasoconstriction may already be present. Nitrite is a powerful reducing agent and converts hæmoglobin to methæmoglobin. Cyanosis due to this latter pigment is a characteristic feature of nitrite poisoning. This action of nitrite is applied therapeutically

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in the treatment of cyanide poisoning (see below). The methæmoglobin can be changed to hæmoglobin by the use of methylene blue. Severe nitrite poisoning has resulted from the use of bis-muth subnitrate in the treatment of infantile gastro-enteritis and nitrite poisoning has also occurred in babies whose feeds have been prepared with water heavily contaminated with nitrate. In both these circumstances nitrate is converted by organismal action in the gut of the infant to nitrite and absorption of the latter ion has resulted in poisoning.

Workers in the nitroglycerine industry are familiar with the throbbing headache and flushing due to absorption of the liquid through the skin, but tolerance quickly develops to these side-effects.

*Preparations, Doses and Administration.* Only Glyceryl Trinitrate is now included in the British Pharmacopœia. Amyl nitrite is still used in therapeutics and octyl nitrite is occasionally used in place of amyl nitrite. Of the longer-acting nitrites only PETN is still in common use while sodium nitrite is now used therapeutically only in the treatment of cyanide poisoning.

*Glyceryl Trinitrate* is a yellow explosive liquid which is dispensed in Tablets, with Mannitol as the basis, each containing 0.5 mg. of the drug. The tablet is chewed and the fragments allowed to melt under the tongue so that the Glyceryl Trinitrate is absorbed from the buccal mucosa. Thus administered its action begins in 1-2 minutes, is maximal in about 5 minutes and lasts for 15 minutes. The drug is also absorbed from the gastro-intestinal tract, but too slowly to be effective in the treatment of angina pectoris. It is also absorbed through the skin and this is a matter of importance to those who handle the substance in industry.

*Amyl Nitrite* is a clear, yellow, volatile liquid with a characteristic pungent odour of pear drops. It is administered by inhalation and is dispensed for use in fine glass ampoules covered in fabric (vitrellæ) which are crushed in a handkerchief and the contents inhaled. The dose is 0.12-0.3 ml. Thus administered the action of amyl nitrite begins in 15 seconds, is maximal in 1-2 minutes and lasts for not more than 5 minutes. It is ineffective when swallowed because it is destroyed by the gastric juice.

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*Octyl Nitrite* is administered in the same manner and in the same dose. It acts for slightly longer than amyl nitrite and is less likely to produce unpleasant side-effects.

*PETN* is a white insoluble powder. It is explosive. *PETN* is dispensed diluted with lactose in tablets containing 10 mg. or 30 mg. It is adequately absorbed from the gastro-intestinal tract and its action is prolonged for up to 6 hours. It is also absorbed from the buccal mucosa. The daily dose is up to 180 mg. in divided doses.

*Erythrityl Tetranitrate* and *Mannitol Hexanitrate* are now seldom used but resemble *PETN* in being slowly absorbed from the gut and producing a prolonged nitrite effect.

Sodium nitrite is used therapeutically only in the treatment of cyanide poisoning when 0.5 G. made up to 20 ml. of solution, freshly prepared, is injected slowly intravenously (see below).

*Metabolic Fate.* After absorption nitrite ion and nitroglycerin rapidly disappear from the blood. About 60 per cent of absorbed nitrite is metabolised in an unknown manner and the remainder is excreted in the urine. The amyl radical of amyl nitrite is partly excreted by the lungs and partly oxidised.

The organic nitrates are partly converted to nitrite in the body, but it is uncertain where this change occurs and whether the nitrite so formed is wholly responsible for the spasmolytic action of organic nitrates. The matter requires further investigation.

**THERAPEUTIC USES.** The most important use of nitrites is in the treatment of angina pectoris and the drug of choice is nitroglycerin. The tablet should be chewed and held under the tongue as early as possible in the attack. The drug is also very useful taken in the same manner in preventing the occurrence of angina if the patient is about to undertake effort which he knows by experience is likely to provoke an attack. The tablet may then be chewed a few minutes before the expected time of occurrence of the pain.

The correct dose is the amount required to prevent or relieve the pain; some patients may find that a half tablet suffices whereas others may require two tablets at a time. Throbbing headache,

dizziness and flushing may accompany the use of larger doses of the drug, and occasionally a patient may report that he is obliged to assume the recumbent posture to obtain relief from these side-effects. It is important to remember that though tolerance to such side-effects may be quickly acquired it is seldom that the phenomenon of "tolerance" causes a parallel reduction in the efficacy of the drug to relieve anginal pain. Amyl nitrite is a less satisfactory drug in the treatment of the acute attack of angina pectoris. Its effect is transient, the side-effects are more prominent, and the strong odour and mode of administration are likely to attract the attention of bystanders. For these reasons most patients much prefer nitroglycerin. Nevertheless amyl nitrite may give dramatic relief in some cases of angina, especially attacks occurring at rest. The prolonged pain of myocardial infarction is not relieved by either remedy.

The long-acting nitrites have been used in an attempt to reduce the frequency of attacks and to improve the patient's effort tolerance. In the past sodium nitrite, erythrityl tetranitrate and mannitol hexanitrate have been used with little success. Current opinion favours PETN as the most suitable drug of this type. It is given in divided doses of up to 180 mg. daily at 6- to 8-hourly intervals. A proportion of patients seem to derive benefit from this therapy along with nitroglycerin as needed. PETN or other long-acting nitrites are of no value in providing immediate relief in the acute attack.

*Other Uses of Nitrites.* Smooth muscle spasm may be abolished by nitrite: amyl nitrite or glyceryl trinitrate are sometimes effective in relieving lead colic, biliary colic and ureteric colic, but the effect is usually transient. In patients with achalasia of the cardia, amyl nitrite or octyl nitrite may be useful but tolerance tends to develop rather quickly.

Bronchial spasm does not usually respond to treatment with nitrite.

Hiccoughs may be dramatically relieved by the inhalation of amyl nitrite, and this remedy is always worth trying in prolonged attacks. The mode of action is unknown. In cyanide poisoning 0.5 G. of sodium nitrite given intravenously in 20 ml. of solution



## DILLING'S CLINICAL PHARMACOLOGY

and followed by 12.5 G. of sodium thiosulphate in 50 ml. of solution may prove life saving. The mode of action is to convert hæmoglobin to methæmoglobin which then competes with the cytochrome enzyme system for cyanide ion with the formation of cyanmethæmoglobin. The sodium thiosulphate then converts cyanide which is released by the dissociation of cyanmethæmoglobin, to the relatively non-toxic thiocyanate, and this product is then excreted.

Nitrites were formerly used in the management of arterial hypertension, but their use has now been abandoned.

### KHELLIN

This drug is obtained from the fruit of an eastern Mediterranean plant, *Ammi visnaga*. The pure substance occurs as insoluble needle crystals with a bitter taste ; it has been synthesised.

**PHARMACOLOGICAL ACTIONS.** Khellin relaxes smooth muscle including that of blood vessels, bronchi and the intestine. It is said to relax selectively the coronary vessels without appreciable change in blood pressure or heart rate. In experimental animals it is a powerful bronchial dilator.

*Preparations, Doses and Administration.* Khellin is usually dispensed in tablets containing 25 mg. or 50 mg. for oral use. It may also be given in a suppository or by intramuscular injection. The usual daily dose is 100-300 mg. The drug is readily absorbed from the gastro-intestinal tract and also after intramuscular injection, and is widely distributed throughout the tissues. It is slowly destroyed in the body. Hence its action is prolonged and cumulative effects may occur.

*Side-effects.* The most important side-effects are nausea and vomiting after oral administration of the drug. These symptoms occur with such regularity as to interfere seriously with its use. Vertigo, insomnia, and a maculopapular rash have also been noted.

**THERAPEUTIC USES.** Khellin has been employed mainly in the treatment of angina pectoris and bronchial asthma. In both conditions there are conflicting reports about its usefulness. It has

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not found favour in this country on account of its doubtful therapeutic value and the high incidence of nausea and vomiting following its use.

### THE VERATRUM ALKALOIDS

Crude extracts of veratrum and related plants have long been used in the treatment of pregnancy toxæmia and other vascular disorders but in recent years there has been renewed interest in the hypotensive action of these alkaloids. Many alkaloids have been isolated and identified; the most active alkaloids are related chemically to the aglycones of the cardiac glycosides.

**PHARMACOLOGICAL ACTIONS.** The actions of the veratrum alkaloids are complex and have not been fully elucidated. Only the more important actions applicable to man will be discussed. The alkaloids produce a fall in blood pressure, bradycardia, respiratory depression, emesis and typical alteration in the excitability of muscle and nerve. The last effect is of pharmacological interest in relation to the mode of action of the alkaloids, but has no clinical application and will be referred to only briefly.

*Cardiovascular Actions.* The main effects of therapeutic doses of veratrum are a fall in blood pressure and a decrease in heart rate. Both systolic and diastolic levels are lowered in proportion to the dose administered. This effect on blood pressure can be reversed by sympathomimetic vasoconstrictors, but is only slightly affected by atropine. Atropine, however, completely reverses the bradycardia. The fall in blood pressure is due to widespread vasodilatation which includes the renal and cerebral vessels. The action is a reflex one due to stimulation of the vagal afferent nerve endings in the left ventricle, lungs and possibly the carotid sinus and carotid body. The efferent fibres concerned in producing the peripheral vasodilatation have not been accurately determined, but the vagus efferent pathway is responsible for the bradycardia. The two effects constitute the Bezold-Jarisch reflex.

*Respiration.* The respiratory rate is slowed by veratrum alkaloids and toxic doses produce respiratory arrest. The effect is reflex from stimulation of pulmonary stretch receptors, but in therapeutic doses in man it is unimportant.

*Emesis.* This action of the veratrum alkaloids is important as it

usually parallels the hypotensive effect and often seriously interferes with effective oral medication. It tends to be more marked after oral administration. In the cat, vomiting is due to stimulation of afferent receptors in the nodose ganglion of the vagus nerve.

*Muscle and Nerve.* Veratrum alkaloids produce self-sustained repetitive discharges from skeletal muscle and motor nerves following a single stimulus. The effect on muscle is reflected on the myogram as a prolonged tetanus. This action has no clinical application, but it is of interest as a similar action on sensory nerve endings determines the reflex effects referred to above.

*Toxic Effects.* Reference has already been made to the vomiting which so often accompanies the hypotension induced by veratrum alkaloids and nausea, salivation and retching are often troublesome. These effects tend to be more marked when the drug is given by mouth. Tingling of the mouth and fingers, and burning sensations in the face are not uncommon while blurred vision sometimes occurs. Cardiac irregularities and respiratory depression are rarely seen with therapeutic doses.

*Preparations, Doses, Duration of Action and Fate.* There are no official preparations of veratrum but several are available commercially. "Veriloid" is a mixture of alkaloids from *veratrum viride* biologically standardised. It is available as tablets each containing 1 or 2 mg. and also as a solution for injection containing 0.4 mg. per ml. in 0.25 per cent acetic acid. The total daily dose by mouth varies from patient to patient, but is usually within the range of 10–20 mg. It may be given intravenously or intramuscularly as an emergency measure, the dose being controlled by careful observation of the blood pressure.

A mixture of protoveratrine A and B from *veratrum album* is also available as tablets, each containing 0.25 mg., or as a solution containing 0.1 mg. per ml. for parenteral injection. The daily dose depends upon the response of the patient.

"Veratrone" is an older preparation of mixed alkaloids from *veratrum viride* which contains 2.5 mg. per ml. and can be given by mouth or by injection.

The hypotensive action of veratrum alkaloids is short-lived and repeated administration is necessary over the twenty-four hours

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to maintain the effect. Little is known about the absorption of the drug from the gut but the oral dose is about ten times as great as the effective parenteral dose. Only a small fraction is excreted in the urine and most of the drug is quickly inactivated in the body.

**THERAPEUTIC USES.** Veratrum preparations have been used in the treatment of arterial hypertension but the accompanying nausea and vomiting have often prevented successful treatment. The short-lived action makes frequent doses during the twenty-four-hour period necessary.

Parenteral use of these drugs is reserved for hypertensive crises, though ganglionic blocking agents are more often used for this purpose nowadays.

"Veratrone" has for long been used in the treatment of eclampsia, but it is doubtful if this preparation or other veratrum preparations has any advantage over other hypotensive remedies in this condition.

At present the general impression is that veratrum alkaloids are less valuable than other hypotensive remedies in the treatment of severe hypertension.

## RAUWOLFIA

Preparations of the root of *Rauwolfia serpentina* have been used in India for many years in the treatment of a variety of diseases, and the drug has been studied by Indian pharmacologists for a quarter of a century. It was introduced into Western medicine in 1952, and is now used as a hypotensive remedy and in the treatment of psychiatric disorders.

**Composition.** Rauwolfia contains a great many alkaloids. Those of therapeutic importance are reserpine, rescinnamine and deserpidine, all of which have the same type of pharmacological action. Preparations of rauwolfia root have essentially the same effects in man as the pure alkaloids mentioned above.

**PHARMACOLOGICAL ACTIONS.** Rauwolfia exhibits a complex pattern of activity in man. The actions upon which its therapeutic usefulness depends are exerted on the central nervous system and cardiovascular system. It has a sedative effect of a

peculiar kind, lowers arterial blood pressure and causes bradycardia. Accompanying these useful actions are a wide variety of side-effects.

*Action on the Central Nervous System.* Rauwolfia has a sedative action on the central nervous system, but it is not a true hypnotic and even large doses do not produce anaesthesia. Subjects under its influence are lethargic and apathetic, tend to sleep longer than usual but can readily be aroused. There is diminished spontaneous motor activity. The drug is not an analgesic and it possesses no anticonvulsant properties. Indeed the reverse is true. These actions are of value in the treatment of agitated psychotic patients. Some subjects develop severe mental depression after treatment with rauwolfia, and with large doses a Parkinsonian syndrome regularly develops. These effects are discussed below.

*Action on the Cardiovascular System.* Rauwolfia leads to a lowering of blood pressure and bradycardia. The latter effect is seen more consistently than the former. The fall in blood pressure affects both systolic and diastolic levels and tends to be more marked when the blood pressure is raised than in normotensive subjects. Little change occurs in the cardiac output and no consistent changes in renal or cerebral blood flow have been noted. Postural hypotension is uncommon with oral treatment, but may occur when large doses are given parenterally. Increase in the dose of the drug does not usually result in a further reduction in the blood pressure but tends to prolong the duration of effect.

*Side-effects and Toxic Effects.* Some side-effects are invariable accompaniments of rauwolfia therapy. When the drug is used as a hypotensive agent in doses exceeding 0.5 mg. reserpine daily apathy and inability to concentrate may occur. The most serious effect is the occurrence of mental depression in from 5 to 20 per cent of subjects. The patient tends to recover only slowly when the drug is withdrawn and psychiatric treatment may be required in the severe cases. Suicide has occurred during the course of reserpine-induced depression. When large doses of reserpine are administered over a prolonged period of time Parkinsonism results. It disappears, sometimes slowly, when the drug is discontinued. Miosis and respiratory depression also occur with therapeutic doses but they are not prominent features in man.

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Nasal and conjunctival congestion, with flushing of the face and neck, are common side-effects. The nasal congestion is resistant to sympathomimetic vasoconstrictors and to antihistaminics.

Salivation, nausea, vomiting and epigastric discomfort may occur when large doses of the drug are given by mouth, and on rare occasions gastroduodenal bleeding has been induced. A laxative effect is common at all dosage levels..

Increased appetite and increase in weight are often seen, and these effects may be marked in mentally disturbed patients. Salt and water retention with œdema have sometimes been noted, and congestive heart failure may be precipitated in patients with severe hypertensive heart disease.

*Mode of Action.* It is generally held that the main action of rauwolfia is exerted at subcortical and hypothalamic levels. Depression of somatic nervous pathways at these sites accounts for the sedative effects, and inhibition of sympathetic outflow at hypothalamic level leads to vasodilatation with consequent lowering of blood pressure. The bradycardia is also thought to be due to central sympathetic inhibition. In addition, however, reserpine has a direct relaxant effect upon arteriolar muscle and is a weak adrenolytic agent and these actions may account in part for the vasodilatation induced by the drug. The mechanism of action upon the gastro-intestinal tract and how the drug produces its metabolic effects are not yet known.

*Preparations, Absorption and Fate.* The official preparation of Rauwolfia is Reserpine given by mouth as Tablets in a daily dose of 0.25–1 mg. Reserpine is marketed as tablets in varying strengths from 0.1 mg to 4 mg. and as a solution for injection containing 1 mg. or 2.5 mg. per ml. of solution. A proprietary preparation of whole root, "Raudixin", is available as tablets, each containing 50 mg. "Rauwiloid" is a refined mixture of alkaloids and is available for oral use in tablets of 2 mg. strength. Reserpine is adequately absorbed from the gut, but its fate in the body is not accurately known. There is a characteristic latent period before its effects become manifest, and even after intravenous administration several hours elapse before its action is maximal. The effects of

reserpine are prolonged and last for several days or even longer after the drug is withdrawn, depending upon the daily dose and duration of therapy. The mechanisms involved have not yet been defined.

**THERAPEUTIC USES.** *As a Hypotensive Agent.* Rauwolfia is used in the treatment of arterial hypertension. When the drug was first introduced doses of the order of 1 mg. of reserpine daily (or corresponding doses of the impure preparations) were used, but the results in severe hypertensive disease were not impressive. A reduction of the blood pressure to normal levels was rarely obtained though symptomatic improvement was often seen. Side-effects were often troublesome, especially mental depression which occurred in about 20 per cent of patients treated. The current tendency is to use reserpine in a daily dose not exceeding 0.5 mg. combined with other hypotensive remedies such as mecamylamine. By this means the wide fluctuations in the blood pressure which occur when a ganglion-blocking agent is used alone may be lessened. Further, a reduction in the dose of mecamylamine may be achieved with consequent reduction in the incidence and severity of side-effects.

*In Psychiatric Practice.* Reserpine is widely used in the treatment of agitated psychotic states and in schizophrenia. Daily doses greatly exceeding those employed in the treatment of arterial hypertension are used and 10 mg. or more of reserpine may be required. Treatment is often begun with parenteral administration of reserpine. In mental institutions the drug is a valuable adjunct in the management of such patients; and although it does not cure the illness it makes the patient much more accessible to other forms of psychotherapy.

The status of rauwolfia in the treatment of arterial hypertension and the psychoses has not yet been finally determined.

*Other Uses.* Rauwolfia has been used for its sedative effect in the neuroses and various psychosomatic disorders, but it is of doubtful value in these conditions.

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### HYDRALLAZINE

This drug, which is chemically 1-hydrazinophthalazine ("Apresoline"), and its congener 1:4-dihydrazinophthalazine ("Nepresol") have been used as hypotensive agents in recent years. The effects of the two compounds do not differ significantly.

**PHARMACOLOGICAL ACTIONS.** Hydrallazine lowers blood pressure in hypertensive and normotensive subjects. The effect is slow in onset but prolonged. Even after intravenous injection there is a delay of ten to twenty minutes before the blood pressure falls, and after oral administration the delay is even greater. The effect lasts for several hours depending upon the dose and route of administration. Accompanying the fall in blood pressure there is an increase in the renal blood flow without much change in renal function. The increased renal blood flow is a unique effect among hypotensive agents.

The cardiac output and heart rate are increased by hydrallazine and these effects come on more quickly and are less persistent than the fall in blood pressure; they can be prevented by ganglion-blocking agents. Hydrallazine has no direct effect on heart muscle.

*Mode of Action.* The mode of action of hydrallazine has not been clearly defined. There is no doubt that the fall in blood pressure is due to arteriolar dilatation and that this is in part due to a direct relaxant effect of the drug on the arterioles. Hydrallazine also antagonises the action of many vasoconstrictor substances including noradrenaline and this effect may also contribute to the vasodilatation. It has also been held that central depression of vasomotor tone plays an important part, but this view awaits confirmation. The cause of the increased cardiac output and tachycardia is sympathetic stimulation, but whether this is a reflex action or a central one remains to be determined.

*Toxic Effects.* These were frequent when relatively large doses of hydrallazine were used but are much fewer with modern low-



dosage therapy. The commonest side-effect is throbbing headache which often disappears, however, as treatment is continued. Palpitation, flushing of the skin of the face and nasal congestion are not uncommon. Nausea, vomiting, general malaise and extreme lethargy are sometimes seen, and these last symptoms may be the most troublesome. Erythematous skin rashes and œdema have also been reported.

In some patients treated with large doses for a prolonged period a syndrome resembling rheumatoid arthritis has occurred, and systemic lupus erythematosus has also been reported in such patients.

*Preparations, Doses and Fate.* Hydrallazine is available in tablets containing 25 mg. or 50 mg. and a solution for injection containing 20 mg. per ml. is also marketed. The drug is not included in the British Pharmacopœia. Hydrallazine is well absorbed from the gastro-intestinal tract, and then almost completely metabolised in the body. Only a small fraction of the dose can be recovered either free or conjugated in the urine. The delayed onset of action and long duration of action of the drug have already been noted.

**THERAPEUTIC USES.** Hydrallazine has been used in a daily dose of up to 1 G. in the treatment of arterial hypertension, but the incidence of side-effects is high and the initial blood pressure lowering effect is not well sustained. Its use as the sole agent in the treatment of hypertension has been abandoned. In small doses, usually not exceeding 100 mg. daily, it has been employed along with ganglion-blocking agents and reserpine, but the value of such combinations of drugs in the treatment of severe hypertension has not yet been assessed. A commercial preparation containing reserpine and "Nepresol" is also available for use. There is some evidence that hydrallazine in conjunction with other hypotensive measures may be especially useful in patients with arterial hypertension complicated by impairment of renal function.

## CHAPTER 11

### DRUGS ACTING ON THE RESPIRATORY SYSTEM

INTRODUCTION. The tissues of the respiratory tract—like many others in the body—are liable to *infections*, and these are often treated successfully with antibiotics and sulphonamides. Apart from specific treatment of this type, the scope of drug therapy in the respiratory system is limited. In general it is directed to producing relaxation of involuntary muscle in the terminal bronchi and bronchioles (relief of asthma) and to altering the quantity or quality of the respiratory tract fluid (the function of expectorants). Drugs which abolish cough (cough suppressants) are of course important, but these palliatives act not on the lungs but centrally on the cough centre in the medulla; alternatively they are demulcents (such as gelatin pastilles) which soothe the mucosa of the palate and pharynx, where irritation may cause troublesome coughing even though the respiratory tract proper is not involved or has recovered from the effects of bacterial invasion.

#### BRONCHIAL SECRETION AND EXPECTORANTS

In normal people there is no excess of respiratory tract fluid. An increase in the volume of this secretion occurs—as part of a protective reflex—if irritant gases or particulate matter are inhaled. A response of this kind is clearly desirable as a means of physical protection of the bronchial mucosa. Stimulation of the vagus—the secretomotor nerve supply to the bronchi—also causes increased secretion. Further, this effect is sometimes produced reflexly—as a consequence of events which begin elsewhere: if there is severe nausea from gastric irritation, some excess of mucus may be coughed up from the lungs. Formerly this was applied therapeutically: slow-acting emetics were given to excite reflexly an outpouring of bronchial mucus which was

evacuated from the respiratory tract by coughing between the bouts of vomiting—an old-fashioned domestic remedy for “croup”. Out of this experience there grew up a belief that emetics could be used in very small doses—amounts that do not even cause nausea—to promote an increased flow of bronchial secretion. Proof that such an action occurs is still awaited. The conditions under which these drugs are given may well account for failure: only small doses are prescribed, and the drug is so thoroughly diluted by food and secretion in the stomach that its action on the gastric mucosa is likely to be negligible. Ammonium bicarbonate, ammonium chloride, and suitable preparations of ipecacuanha, senega and squill make up this group of reflex expectorants. Physicians who continue to prescribe these drugs claim that even if there is no proof of an increase in the volume of sputum, the preparations confer benefits of some other kind—perhaps by altering the physical character of the sputum. This view is speculative: experimental work and direct observations on the viscosity of sputum lend no support to those who use reflex expectorants empirically.

A better case can be made for using potassium iodide or sodium iodide to increase the volume of sputum or to reduce its viscosity. Patients who have an idiosyncrasy to iodides may cough up considerable quantities of respiratory tract fluid—as an accompaniment to excessive salivation, lachrymation, and running at the nose. Of course, it does not necessarily follow that similar effects occur in the respiratory tract in the absence of idiosyncrasy: indeed if there is no perceptible rhinorrhœa it seems improbable (though not impossible) that any quantitative change is occurring in other secretions in the respiratory tract. It has long been known that iodides are excreted by the bronchial mucosa, as indeed they are excreted by many other glandular tissues. This observation in itself is of limited importance to the pharmacologist and to the clinician. However, it is possible that potassium iodide sometimes reduces the viscosity of the sputum. Should this occur the change may have therapeutic importance, and there is therefore a *prima facie* case for giving potassium iodide when patients have a viscid sputum and some difficulty in expectoration.

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The mucosa of the respiratory tract is kept constantly moist by the secretion of a watery mucoïd fluid. This is being constantly cleared from the bronchi and trachea: ciliary action causes the fluid to move slowly but continuously upwards to the pharynx where it mixes with the pharyngeal and salivary secretions and is normally swallowed. Such secretion may be regarded as the "insensible" secretion of the healthy respiratory tract and is analogous to the "insensible perspiration" of the skin.

A chronic productive cough is usually attributable to chronic bronchitis: characteristically the patient coughs up a few fluid ounces of sputum every day. Other considerations apart, this abnormal volume of secretion in the respiratory passages may create a mechanical hazard: it may obstruct the smaller bronchi and thus hinder ventilation of lung parenchyma, and this in turn may lead to persistent coughing in the attempt to maintain a clear air-way. Although brief spells of coughing are harmless and indeed beneficial in some circumstances, *persistent* coughing over a prolonged period often has serious consequences: in particular it predisposes to the onset of generalised emphysema—a condition which may be followed by severe cardiac embarrassment.

Reference has been made above to some of the physiological and pharmacological aspects of the concept—an *expectorant*. Any drug that helps a patient to evacuate his sputum might be designated an expectorant by clinicians; but the term is conventionally restricted to those drugs which facilitate expectoration by their action in liquefying the secretion. In this narrower sense it is doubtful if any drug has a true expectorant action when used therapeutically *in man*. In brief, there is the phenomenon of alterations in bronchial secretion that can be effected reflexly: these have been mentioned above. The crux of the matter is this: can such changes be demonstrated as a result of giving "reflex expectorants" (short of nauseating doses) to human patients—as distinct from experimental animals? No evidence of this alleged expectorant action has yet been produced by the technique of clinical trials. It may be that this is an example of therapy founded on mere supposition and a practice which cannot be justified when the claims are examined critically and the clinical results are measured. In the absence of a radical cure for bron-

chitis it is easy to understand the reluctance of patients to abandon the use of traditional "remedies". Further, it has been shown that in treatment intended to reduce the frequency of coughing, if the doctor gives his patient an *inert* substance there may be important benefits though these must be psychological in origin and not pharmacological.

The drugs and other measures commonly used in medical practice to promote expectoration are considered individually below, and their other pharmacological actions are also mentioned.

POTASSIUM IODIDE is a colourless, odourless, crystalline or white granular powder; it is soluble in water and has a slightly bitter saline taste. The salt is produced chemically in commerce. Iodides are readily absorbed from the intestine and are then distributed widely in the body in small amounts in a manner similar to chloride. They are found in all extracellular fluids except for cerebrospinal fluid. Iodides are present in the secretions of all externally secreting glands, sometimes being concentrated considerably—up to thirty times in the gastric juice and saliva. Some iodine is utilised by the thyroid gland to form thyroid hormone, but nearly all the remaining iodide is excreted by the kidney.

Potassium iodide has been found in bronchial secretions obtained at bronchoscopy fifteen to twenty-five minutes after oral or intravenous administration. It has been held that because potassium iodide is excreted by the bronchial glands the salt must have an expectorant effect in one of two ways: by increasing the amount of bronchial secretion by simple dilution, or by alternatively causing a change in the physical properties of the secretion (for example lowering of viscosity). Although it has been established that an increase in the output of sputum can occur in some patients with chronic bronchitis while on potassium iodide, it is not known whether this effect is sufficiently common to be therapeutically significant.

Further experimental studies are needed for a precise assessment of the therapeutic value of potassium iodide in bronchitis and in other diseases of the lungs. Conclusions must necessarily be based on the results of well-designed experiments. The empirical

## DRUGS ACTING ON THE RESPIRATORY SYSTEM

uses of potassium iodide in the past provide ample justification for attempting to analyse its mode of action. For example the manifestations of syphilis in its secondary and tertiary forms may be abolished by giving sodium or potassium iodide. The iodides are not toxic to the *Treponema pallidum*, but they are remarkably effective in promoting the rapid resolution of gummata—the granulomata of tertiary syphilis (1–2 G. three times a day by mouth). This action has been attributed to the power of iodides to lower the antitryptic power of serum and to convert unsaturated lipoids (which are antitryptic) into saturated forms which do not resist autolysis. Thus iodides which diffuse readily into pathological tissues may promote absorption, both by increasing the autolytic power of serum and also by lowering the resistance of the tissues to enzyme action. Although this explanation of the mode of action of iodides in dispersing large masses of granulation tissue may be disputed, the spectacular effect of the treatment cannot be doubted. Thus empirical practice fully warrants trials of iodides in chronic inflammatory diseases as a form of symptomatic treatment. Many practitioners still consider it wise to give potassium iodide for a few weeks before giving a quick-acting agent like penicillin in tertiary syphilis, to minimise the risk of a local reaction. Sequelæ of the Jarisch-Herxheimer type are especially dangerous in syphilitic aortitis, where the ostia of the coronary arteries may be involved, or in late manifestations of neurosyphilis.

As the iodides of sodium and potassium appear to have a lytic action on the granulation tissue which forms in the course of chronic inflammation, these drugs were sometimes used in chronic pulmonary tuberculosis. It is open to doubt whether this is a rational approach to treatment: the management of tuberculosis and other infective foci on conservative lines aims at preventing the breakdown of natural barriers to the spread of micro-organisms and thus “containing” the infection locally. If it is established that iodides cause softening or liquefaction of tuberculous granulation tissue, their use in this infection is likely to be harmful rather than helpful. Iodide therapy has been advocated as a supplement to specific remedies, but the desired effect on connective tissue at the site of the infection is more

readily obtained from cortisone—on the rare occasions when this ancillary method of treatment is deemed desirable.

Prior to thyroidectomy Potassium Iodide, 60 mg. twice daily by mouth, may be given for 10 to 14 days to counter the increased vascularity, and especially if goitrogenic drugs have been given (p. 359).

*Toxic Effects.* (i) Occasionally patients show a marked *hypersensitivity* to iodides, with an angioneurotic or serum-sickness type of reaction. Adrenaline Injection 1/1,000 0.5–1 ml. should be given intramuscularly to abolish or modify existing lesions attributable to local vasodilation; and as a preventive against recurrence of such complications one of the long-acting antihistamines can be given orally (p. 284).

(ii) *Iodism.* This term is reserved for idiosyncratic reactions to iodides or to iodine. The symptoms are usually mild and are easily recognised. They simulate an acute coryza: the eyes become suffused and there is a watery rhinorrhœa; salivation increases and a metallic taste and a burning sensation may be felt in the mouth and throat. It was probably the associated increase in bronchial secretion—typical of iodism—that suggested the use of iodides as expectorants. The parotid and submaxillary salivary glands may enlarge. Skin eruptions are not uncommon and they may be severe with the formation of bullæ. Nausea and vomiting are common: gastric irritation may be partly attributable to the release of iodine in the stomach by the action of free hydrochloric acid on the iodide, but as this also occurs in the absence of iodism, it would appear that the gastric symptoms of idiosyncrasy indicate involvement of the tissues of the stomach wall in an abnormal and widespread reaction of the body cells. If the symptoms of iodism are mild, it may be practicable to induce tolerance by continuing to give the drug over a period of several days. Bold measures such as doubling the dose are to be deprecated: the circumstances in the individual patient must be reviewed, and if dangerous developments seem imminent iodide must be stopped and abundant fluid and sodium chloride given to promote excretion.

Prolonged administration of iodide in excess of therapeutic requirements may lead to gastro-intestinal upsets with loss of

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appetite and chronic malnutrition; mental apathy and sexual impotence have also been reported.

*Preparations and Dosage.* Potassium Iodide: dose as an expectorant, 0.3–2 G. orally.

Ammoniated Mixture of Potassium Iodide, 15–30 ml.

SODIUM IODIDE is deliquescent in moist air. It has properties similar to those of potassium iodide—with which it is interchangeable for clinical use and it is given in the same doses. Traces of sodium iodide have been added to table salt (0.01 per cent) for the prevention of goitre in endemic areas. Solutions of sodium iodide can be used as a radio-opaque medium in cystography (5–10 per cent), and in retrograde pyelography (up to 15 per cent).

AMMONIUM SALTS. After ingestion ammonium salts are liable to cause gastric irritation and nausea. Hence they are used as expectorants in the belief that this gastric irritation can *reflexly* increase bronchial secretion. Although an increase in respiratory tract fluid has been demonstrated following their use in animal experiments, reliable clinical studies in patients with chronic bronchitis have failed to show any expectorant action. The positive results reported from animal experiments were obtained only by giving extremely large doses, and these observations cannot be applied in this crude form to human therapeutics. It is noteworthy that when ammonium chloride is given to patients for other purposes (such as acidification of the urine) an expectorant action is rarely, if ever, produced.

*Ammonium Chloride* is an odourless, white, crystalline or granular powder, soluble in water; it has an unpleasant saline taste. The irritant action in the stomach is a disadvantage when ammonium chloride is given for its systemic effects, and it is therefore often given in capsules. On absorption from the bowel the ammonium ion is converted to urea in the liver. The anion that is liberated displaces bicarbonate and thus tends to cause a metabolic acidosis, and a diuresis follows (p. 35). The ammonium ion is toxic to the central nervous system: in particular it stimulates the spinal cord and the vasomotor and respiratory centres in the medulla. High concentrations can cause convulsions and respiratory arrest. There is a weak curare-like effect on voluntary muscle.



## DILLING'S CLINICAL PHARMACOLOGY

As an expectorant Ammonium Chloride is usually dispensed in mixtures with an individual dose of 0.3 G. There is also a Mixture of Ammonium Chloride and Morphine, (dose 15-30 ml.). This represents an old-fashioned type of "expectorant mixture". It is intended to loosen the sputum (reflex action of the ammonium chloride) and also to suppress the cough (depressant action of morphine on the cough centre in the medulla). The rationale is open to doubt: to increase the amount of sputum and simultaneously to depress the cough reflex is an example of therapeutic incompatibility. In practice such benefits as are obtained from the Mixture are due to the sedative effects of morphine: no expectorant effect—and therefore no embarrassment—is perceptible.

*Ammonium Bicarbonate* is a white, crystalline powder, soluble in water, with a slight ammoniacal odour and a pungent taste. It is included in many mixtures in the belief it has an expectorant action similar to that of ammonium chloride. It has fallen into disuse and it has been deleted from the B.P. 1958.

As ammonium carbonate is largely composed of the bicarbonate, for some years ammonium bicarbonate has been dispensed when the carbonate is prescribed.

*Ipecacuanha*. Pharmaceutical preparations are made from the dried root. The active principles are the alkaloids emetine, cephaeline and psychotrine. Although ipecacuanha is classed as an expectorant, it is mainly important as the source of emetine—used by intramuscular injection in the treatment of amœbic dysentery (p. 561). As the name implies, emetine and preparations which contain this alkaloid cause vomiting when they are taken by mouth. This action is attributable to the irritant effect of emetine and cephaeline on the gastric mucosa. It is said that on absorption these alkaloids also stimulate the vomiting centre in the medulla and that this contributes to the emetic action. This is difficult to reconcile with the fact that a dose of 60 mg. of emetine hydrochloride given intramuscularly fails to produce nausea, and this dose represents about twice the quantity of emetine contained in a full emetic dose of Tincture of Ipecacuanha for oral use.

Ipecacuanha is used as a "reflex expectorant" but no convincing evidence has been produced that this drug affects the volume of sputum. If nauseating doses of ipecacuanha are given the patient may develop increased sweating ("cold sweats"). This action accounts for the diaphoretic and antipyretic actions of ipecacuanha.

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When the compound powder of opium and ipecacuanha (Dover's Powder) is used, the intention is to combine two drugs which cause sweating, as opium causes flushing of the skin and "warm sweats". It is open to doubt whether in fact the ipecacuanha serves any useful purpose in this compound preparation.

*Squill and Senega* are still included in some of the expectorant mixtures set out in formularies. They are said to produce reflex bronchial secretion by mild gastric irritation, but their use is based on tradition rather than on evidence of pharmacological action.

*Creosote* was formerly used as an expectorant and pulmonary antiseptic. The rationale was always open to doubt, and it is now regarded as an obsolete drug.

EXPECTORANT DRINKS AND INHÁLATIONS. Patients who suffer from chronic bronchitis and other infections of the respiratory tract are quick to discover the value of copious hot drinks—especially when these are taken on waking after a night's sleep. "Dryness" of the mouth and pharynx is common among these patients—probably in part as a result of mouth breathing; they may also be excessively sensitive to the minor degree of dehydration that occurs normally during 7 or 8 hours sleep. Hot water, tea or lemon juice is taken—as hot as the patient can bear to drink it—by sipping. The cumulative effects of the hot fluid on the mucosa of the fauces and the stomach resemble those of a fomentation. It is likely that part of the benefit derived from this procedure is due to increased secretion in the bronchi brought about reflexly from thermal stimulation of the gastric mucosa. There is no doubt that hot drinks in these circumstances elicit coughing and the evacuation of sputum which would otherwise remain to embarrass the breathing. A tablespoonful of Sodium Chloride Compound Mixture may be added to a tumblerful of hot water or a quarter teaspoonful of sodium bicarbonate may be used alone. Sodium bicarbonate—which is also present in the compound mixture—serves to dissolve sticky mucus in the pharynx.

Droplets of water inhaled as water vapour relieve the dry irritable cough of acute tracheobronchitis by a protective wetting effect and by its soothing and warming action. For the greatest

convenience and efficiency a Maw's Inhaler should be employed (the student can inspect this in the medical wards of the hospital). Alternatively a large (2 pints) jug can be used: it is half-filled with water almost boiling, and a stiff towel is then wrapped round the jug in such a way that the upper part projects beyond the edge of the jug and forms a cuff six inches deep from which the patient inhales the water vapour. Volatile medicaments are usually added to steam inhalations, but it is likely they merely impart a pungent scent which makes the inhalation more acceptable psychologically. Benzoin, Menthol, and Eucalyptus Oil are commonly used. It is advisable to be conservative when adding them, as they can be irritant to the larynx. It is the vehicle (water vapour) that is of prime importance.

**EXPECTORANT AEROSOLS.** An entirely new approach to promoting expectoration is to attempt to liquefy sputum by means of a mucus digest or by using substances that reduce surface tension. Such a preparation is administered as a fine mist or "aerosol"—made by passing oxygen or air under pressure across a fine jet of fluid so that the minute droplets formed are widely dispersed throughout the inhalation. The droplets are only a few microns in size and they are therefore inhaled into the lumina of all the bronchi and bronchioles.

*Trypsin Aerosol.* Trypsin is a naturally-occurring enzyme that is obtained from mammalian pancreas. It is used for its proteolytic action on necrotic material in burns, on blood (for example clot in a hæmothorax), or on mucin when tenacious mucus obstructs bronchi. Its ability to liquefy sputum can readily be demonstrated *in vitro*. Trypsin acts within the fairly narrow range of pH 6·8–7·5, and at body temperature. It is made available with a special phosphate buffer solution of pH 7·1; the trypsin is added to this solution immediately before use. This preparation is comparatively easy to administer but there is an appreciable risk of side-effects—especially substernal irritation and generalised bronchiolar spasm with wheezing—and it is recommended that an antihistamine drug be administered to patients an hour before the aerosol is given. At present the use of aerosols should be limited to otherwise intractable cases.

*Detergent Aerosol.* Theoretically the administration of modern wetting agents by aerosol to patients with chronic bronchitis should help to dilute sputum and make the secretion less sticky. The only preparation of this kind which is in common use has proved rather disappointing, both in clinical practice and on assessment by controlled trials. It is a sterile alkaline solution containing superinone (an ethoxylated *tert.*-octylphenol-formaldehyde polymer) 0.125 per cent, sodium bicarbonate 2 per cent, and glycerin 5 per cent. When its effects have been compared with those of a control no difference has been found; the same degree of improvement results from the aerosol solution without the detergent.

These special aerosol inhalations may help the patient to evacuate sputum simply by virtue of a moistening effect that is proportional to their water content; and an aerosol of water alone might achieve as much. A simple water aerosol is really only the modern equivalent of what is available from using the old-fashioned steam kettle.

Inhalations of *deoxyribonuclease* have been given to liquefy sputum. This preparation, however, can have only a limited use: it acts on pus cells or their residue but has no effect on purely mucoid sputum.

## COUGH SUPPRESSANTS

**INTRODUCTION.** The role of expectorants has already been discussed (p. 323). It is frequently desirable and justifiable to suppress coughing. As coughing is a reflex action, there are theoretically several possible ways of doing this. It is obviously important to safeguard the patient against exposure to external stimuli that promote and perpetuate coughing. There are times when the upper respiratory tract (including the pharynx) is in an irritable state. In these circumstances, excessively dry or cold air, tobacco smoke, irritant gases, foodstuffs such as condiments and toast-crumbs, may excite paroxysms of coughing. Again coughing should not be suppressed prematurely or too rigorously when it is obvious that it is serving a useful purpose: it may be necessary in order to permit the periodic evacuation of infected sputum from bronchiectatic lungs. These general considerations may

suffice to show that before taking steps to suppress coughing, the circumstances affecting the individual patient should be reviewed. It is always worth while to consider simple preventive measures even when there are clear indications for resorting to drugs which depress the cough reflex.

A cough suppressant is valued in proportion to its selectiveness. Many drugs classed as narcotic analgesics can be expected to suppress coughing by an action on the higher centres and by diminishing awareness of sensory stimuli. In practice, however, the drugs chosen as cough suppressants are those which, in convenient doses, reduce the sensitiveness of the cough centre in the medulla; their effects in other parts of the central nervous system and elsewhere are negligible. Thus, for example, alcohol in suitably large doses can act as a cough suppressant, but for obvious reasons it is rarely or never used in this way therapeutically.

The oldest of the drugs which are prescribed to diminish the frequency of coughing is OPIMUM. In suitable preparations it is still widely used; and for this purpose opium is little if at all inferior to modern remedies which include various alkaloids of opium and the morphine substitutes.

The selective action of drugs of the morphine group on the cough centre illustrates one of the most remarkable characteristics of opium and its derivatives. These preparations are effective in suppressing coughing—or greatly reducing the frequency of coughing—and yet they do not produce untoward effects elsewhere, provided of course that the dose of the preparation is skillfully adjusted to meet the circumstances of the case.

In general cough suppressants are strongly indicated when the patient has a dry cough, and especially when such coughing develops on going to bed—often the result of moving from a warm room to a cold bedroom. Another important indication is the need to abolish a cough that causes pain—as for example at the onset of pneumonia and acute pleurisy. Again there may be serious constitutional disease or exhaustion and in these circumstances frequent bouts of coughing may seriously prejudice the patient's chances of recovery.

A preparation which is in common use as a cough suppressant is the Camphorated Tincture of Opium. The camphor and anise

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contained in it are probably valuable only as flavouring agents; the opium itself is the essential ingredient. This preparation is given in a dose of about one teaspoonful (4 ml.) in a little warm water (say 30 ml.). Two or three doses can be taken in the first six hours of therapy and then it can be given two or three times a day. On adding the tincture to water, the mixture becomes opalescent because the camphor is thrown out of solution, but this is a matter of no therapeutic importance. As with other preparations of opium the side-effects include constipation, loss of appetite and slight nausea; the severity of such effects is proportional to the dose and varies too with individual susceptibility. This kind of treatment is best reserved for the evening, and a dose is often taken on retiring to bed: in this way the maximum suppressive action coincides with the greatest need for such treatment; drowsiness from the opium favours the onset of sleep; and side-effects are of course rarely apparent.

DIAMORPHINE HYDROCHLORIDE (Diacetylmorphine Hydrochloride, Heroin). Diamorphine is an alkaloidal base obtained from morphine. In general its actions are similar to those of morphine (p. 245), and its selective depressant action on the cough centre is even more powerful than that of morphine. Diamorphine produces this valuable effect without causing conspicuous side-effects such as nausea, loss of appetite, constipation, etc., which are apt to occur after repeated use of opium, morphine and codeine. Further, diamorphine results in a state of mild euphoria: herein lies its chief danger, for this effect may be so acceptable to the patient that a craving for the drug is quickly created. At the same time, there are occasions when the combined effect of suppressing a useless cough and creating exaltation in mood are highly desirable actions, as for example in a patient with inoperable carcinoma of the lung, where, at a certain stage, addiction to heroin is immaterial. Again, the powerful analgesic action of diamorphine may be invaluable, though the need to control severe pain is an exceptional occurrence except in the later stages of intrathoracic malignant disease. The usual dose of heroin for an adult is 6 mg. It can be given hypodermically, but it is preferable when possible to give it as the Linctus of Heroin (4 ml. contains 3 mg. of

diamorphine hydrochloride) if only because oral medication excites less interest in the patient's mind.

METHADONE is a morphine substitute of high analgesic potency but lacking the sedative effect of morphine. Its cough suppressant action is at least equal to that of morphine, and experimental evidence on man indicates that it may even rank with diamorphine in its power to depress the cough reflex. Its selective action on the nearby respiratory centre makes it necessary to use the drug with due caution. Infants and young children are particularly susceptible to this depressant action on the respiratory centre; this drug is therefore seldom used in pædiatric practice, and it should certainly not be used in obstetric practice because of its depressant effect on foetal respiration. Methadone is a drug of addiction. In adults this drug is nevertheless a valuable cough suppressant for short-term therapy. It is conveniently given as the Linctus of Methadone Hydrochloride (4 ml. contains 2 mg.) and Tablets are available containing 5 mg.

CODEINE PHOSPHATE. Codeine is an alkaloid obtained from opium, but more conveniently prepared by methylation of morphine. It is used therapeutically as the alkaloid or as codeine phosphate. The actions of codeine resemble those of morphine (p. 245) but they are very much weaker: this contrast is particularly obvious in relation to suppression of cough, for the dose of codeine required is at least ten times as great as that of morphine. In these circumstances the universal use of small doses of codeine preparations as cough suppressants is surprising. Critical observation has shown that it is preferable to prescribe opium, morphine or methadone when a cough-suppressant effect is needed. Codeine has the further disadvantage that it usually causes troublesome constipation and (especially in women) it may result in nausea and anorexia. If it is given at all as a cough suppressant, full doses of 60 mg. three or four times daily should be prescribed. Addiction to codeine is a very rare occurrence and not a matter of practical importance. A Syrup of Codeine Phosphate is available; the maximum official dose of 4 ml. which contains only 15 mg. codeine phosphate.

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DEXTROMETHORPHAN HYDROBROMIDE is a synthetic compound which has a rather weak antitussive action comparable to that of codeine. Side-effects on the alimentary canal also resemble those of codeine. Dextromethorphan has a negligible analgesic action and therefore if coughing is accompanied by pain, it is not the drug of choice. It does not cause euphoria and therefore addiction is very unlikely to occur.

PHOLCODINE or Morpholinylethylmorphine represents a real advance on codeine as a cough suppressant. It is effective in smaller doses and does not cause constipation or gastric irritation. Pholcodine has a mild sedative action but it does not cause euphoria and addiction is correspondingly rare. The dose is 5-15 mg. for adults and 4 mg. for children. It is available as a Linctus (4 ml. contain 4 mg.) and as a flavoured Syrup (4 ml. contain 8 mg.).

There are many synthetic morphine substitutes. Nearly all of them were introduced in the hope that they would have some pharmacological and therapeutic advantage over the parent substance. In some respects these objectives have been realised: there are many morphine substitutes which are a potential asset to the clinician who cares to acquire skill in the therapeutic uses of one or more of these compounds. The advantage sometimes lies in the combination of analgesic and cough-suppressant actions. Such therapeutic possibilities—approximating to those of diamorphine—are, however, rarely dissociated from the danger of drug addiction. It is true that this hazard can be exaggerated—especially when a few doses of the drug over a period of a day or two meet the needs of the patient. Nevertheless it is imperative that in using cough-suppressants which are morphine substitutes, the risk of producing addiction should be kept in mind. This group includes *Dihydromorphinone*: it has an analgesic action five times greater than that of morphine and a relatively weak sedative effect; it resembles morphine in its depressant action on the cough centre, but its effects are of shorter duration. As there are safer cough suppressants, dihydromorphinone does not commend itself for routine use therapeutically. Although it is obvious that many narcotic analgesics possess a cough-suppressant action which



is of considerable clinical importance, there are many powerful analgesics in which this action on the cough centre is absent or extremely weak: such are pethidine, phenadoxone, dipipanone and levorphan. It should also be noted that papaverine—an alkaloid of opium—which has a weak spasmolytic action on smooth muscle lacks entirely the cough-suppressant action of morphine.

## SPASMOLYTIC DRUGS

**INTRODUCTION.** Drugs that abolish spasm in smooth muscle may have important therapeutic uses in certain diseases affecting the bronchi. Asthma is a word used to describe a state of widespread constriction of the bronchioles and smaller bronchi: it is attributable to a variety of causes which are fully discussed in standard works on the practice of Medicine. Normally, on expiration there is some narrowing of the lumen of the bronchi, and shortening of the bronchioles; but these changes are slight and the outflow of air is not impeded. In asthma constriction of the bronchi is characteristic of the disability: narrowing of the lumen may be intense and here and there in the bronchial tree complete occlusion may occur. Thus there is obstruction to the flow of air, especially during expiration. (There are, of course, other consequences—which can be explained in terms of patchy collapse of lung parenchyma and supervening infection—but these developments raise pharmacological and therapeutic problems of a different kind.)

A drug which relieves bronchospasm may act in one of several ways. (i) The smooth muscle of the respiratory tract is sensitive to the direct effects of histamine. In the guinea-pig, for example, procedures which release histamine in the animal's tissues readily cause intense bronchiolar spasm which is usually fatal. The guinea-pig can be protected against this histamine effect by giving antihistamines beforehand (p. 279). Unfortunately this experience in the laboratory has little significance in clinical medicine: antihistamines are of very limited value in the management of the asthmatic subject. (ii) As the vagus is the secretomotor nerve to the bronchi, it is reasonable to expect relief of spasm by drugs which block vagal impulses to smooth muscle (p. 120). Beneficial

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effects can in fact be produced by this kind of treatment; belladonna and stramonium preparations are among the oldest of our "asthma cures". In practice, however, there are limitations to the use of such drugs because they simultaneously reduce secretion in the respiratory tract and the patient may then have difficulty in coughing up viscid sputum. (iii) Stimulation of the sympathetic nerve supply to the lungs increases the calibre of the bronchi and under favourable conditions abolishes spasm of the bronchioles. This effect can be achieved by means of the sympathomimetic amines (p. 134), and these drugs when used early, are of great importance therapeutically. (iv) The nervous impulses which affect the secretomotor activity of the respiratory tract are modified by a variety of circumstances, and not the least important of these are psychological factors. Recognition of this situation has led to the empirical use of sedatives such as phenobarbitone. This kind of treatment is essentially preventive in character: the patient's liability to exacerbations of asthma is reduced by the mild depressant action of the sedative on the higher centres of the brain and perhaps a slight effect of the same kind on the respiratory centre in the medulla; there is no direct action on the respiratory tract. (v) Severe asthma which fails to respond to conventional treatment—a condition described clinically as *status asthmaticus*—is now treated by giving corticosteroids. This is the most dependable method of treatment for these patients—who are often seriously ill. The corticosteroids are used empirically in asthma: their mode of action is not understood, but their anti-inflammatory effects are probably of capital importance in relieving widespread congestion and swelling of the bronchial mucosa—conditions which may well become more significant than bronchiolar spasm as causes of dyspnoea and distress in unrelieved asthma.

### SYMPATHOMIMETIC BRONCHODILATOR DRUGS

① ADRENALINE, secreted by the medulla of the adrenal glands, is used either as an acid extract from natural sources or as the synthetic compound. The acid tartrate and hydrochloride are used.

In a sense it is inappropriate to discuss the actions of adrenaline

as pharmacological effects: they are necessarily physiological actions, but with adjustments of dosage a wide range of therapeutic applications are possible when adrenaline is suitably administered. Objective evidence of the bronchodilator action of adrenaline given parenterally or by inhalation is readily obtained by spirometer studies: these show that adrenaline is one of the most potent bronchodilators available. Unlike many other sympathomimetic amines adrenaline has no direct action on the respiratory centre.

In an acute paroxysm of asthma 0.2–0.5 ml. of the Adrenaline Injection (1 in 1,000) is injected subcutaneously. Care must be taken to avoid inadvertently injecting the solution into a vein or venule, as the sudden stimulus to cardiac muscle may produce ventricular fibrillation, an arrhythmia which is often fatal in man. The benefit derived from an injection of adrenaline in asthma appears in two or three minutes. The best results are obtained from *early* administration; the longer the delay in giving treatment, the less likely is the condition to respond favourably. Repeated administration of adrenaline produces a characteristic syndrome of pallor, tremor, fear and restlessness. It is therefore important to avoid excessive quantities. In intractable cases and in status asthmaticus it is often necessary to give repeated injections: when it is obvious that the first dose (0.5 ml.) has not brought adequate relief after 15 minutes further subcutaneous injections of about 0.05 ml. are given every minute until the symptoms have abated or until a total of 5 ml. of the solution has been given. It is generally useless to give doses greater than this because such patients show a diminishing response to the treatment. In these circumstances it is best to withhold further injections of adrenaline for an hour or so. During this time the patient may recover sensitiveness to this preparation and the time can be employed in trying the effects of other drugs. For the reasons stated above adrenaline should not be given intravenously.

Adrenaline can also be given as an inhalation. An aqueous solution (1 per cent) is used, in a hand nebuliser or atomiser; a fine mist is formed, with a particle size of less than 1 micron. Relief is usually obtained as quickly as with a subcutaneous injection—after about five or six inhalations. Further inhalations

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may be taken after a few minutes. In practice this method has much to commend it: a patient can easily carry the nebuliser with him, and the knowledge that an effective remedy is available for immediate use at the onset of a paroxysm is in itself reassuring. It is occasionally necessary to warn patients against resorting to excessive use of the nebuliser as this produces side-effects such as excitement and tremor, and the spasmolytic effect may be impaired when habituation develops. Hand nebulisers are as efficient as those operated by a motor pump or from an oxygen cylinder. When practicable the mouth and pharynx should be rinsed with water after the nebuliser is used, to minimise the amount swallowed.

Adrenaline and Atropine Compound Spray, which contains adrenaline (0.46 per cent), atropine methonitrate (0.114 per cent), and papaverine hydrochloride (0.8 per cent) is unlikely to be more effective than adrenaline alone. Atropine and its derivatives are less effective as bronchodilators than might be expected on theoretical grounds and reference has been made above to their side-effects. Although papaverine has a direct effect on smooth muscle and causes relaxation (p. 257) the action on the bronchi is too weak to be therapeutically significant.

In "chronic asthma" where there is more or less persistent bronchospasm with persistent wheeziness, adrenaline is rarely used because its action is too transient even if it is perceptible. There is sometimes a place for adrenaline mucate ("Hyperduric" adrenaline) which produces a mild but sustained effect and which may therefore prevent minor exacerbations of asthma; the dose is 1 ml. intramuscularly.

EPHEDRINE. This alkaloid occurs naturally in various species of *Ephedra*. It is a sympathomimetic amine. The pharmacological actions of ephedrine resemble those of adrenaline: the comparison is discussed on p. 140. Ephedrine is normally given by mouth; its effects last several hours; it raises the blood-pressure; and it stimulates the brain, causing mild excitement and insomnia.

In the respiratory system ephedrine produces bronchodilatation. The effect is relatively weak but it is sustained, and the drug is therefore better suited to the prevention of asthma than to the

abolition of an established paroxysm. The stimulating action of ephedrine on the respiratory centre contributes to its value in the management of asthmatic patients. When prolonged courses of treatment are given the phenomenon of tachyphylaxis is seen, but sensitiveness to the drug returns if treatment is discontinued for a few days.

Ephedrine is excreted rather slowly by the kidney. Cumulation is not seen if conventional dosage is used, but the drug should not be given after about 4 p.m. in order to avoid insomnia. Side-effects from ephedrine are those of exaggerated sympathetic action (p. 140): it should not be used in patients suffering from hyperthyroidism, hypertension or when digitalis is being used.

Ephedrine Hydrochloride is given to adults in a dose of from 30 to 60 mg. two or three times a day. Children over 7 years of age readily tolerate up to half of the adult dose.

1) METHOXYPHENAMINE is a white, odourless, crystalline powder with a bitter taste. It is a sympathomimetic amine and produces bronchodilatation without troublesome pressor activity or cardiac stimulation. It is useful in chronic asthma in patients who are intolerant of ephedrine or have hypertension. The preparation used is methoxyphenamine hydrochloride, 50-100 mg. by mouth up to 4-hourly.

2) ISOPRENALINE (*Isopropylnoradrenaline*) is a colourless, odourless, crystalline powder, which is soluble in water. Isoprenaline is a sympathomimetic amine with a bronchodilator action greater than that of adrenaline or ephedrine. It is an important drug in the treatment of bronchial asthma, but it has to be used with care because of troublesome side-effects. Patients may complain of giddiness, palpitation, headaches, nervousness, tremor or weakness. Cardiac stimulation causes tachycardia and an increase in cardiac output, but as peripheral vasodilatation also occurs, the diastolic blood pressure falls. It tends to cause excitement by stimulation of the higher centres and as adrenaline provokes the same responses, these two drugs should not be used at the same time. Isoprenaline must be avoided in patients with frank cardiac disease or when hyperthyroidism is present. The

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side-effects disappear as soon as the isoprenaline is withdrawn.

The cardiovascular effects make isoprenaline unsuitable for parenteral administration, but it is generally well tolerated sublingually, provided the dose is adjusted to suit the individual. Patients soon learn their own tolerance and recognise the advantages of carrying tablets which abort minor paroxysms and outweigh other considerations. In chronic asthma isoprenaline is usually used as an adjuvant to spasmolytics with a more prolonged action. The dose of Isoprenaline Sulphate is 5-20 mg. three times a day sublingually, allowing at least three hours to elapse between the larger doses. It is better to start with 5 mg. and to repeat it, if some relief is not obtained in five to ten minutes. The tablets should be allowed to dissolve under the tongue.

Isoprenaline may be given as an inhalation either prophylactically, or for established asthma, using a hand nebuliser or more elaborate aerosol. Toxic reactions are much less common with this method, and it compares favourably with adrenaline. Not more than 1 ml. of a 0.5-3 per cent solution should be used at a time; five to fifteen puffs of the spray usually give relief. The treatment should not be repeated under four hours, unless the patient is closely supervised. An all-glass atomiser is used as contact with metal may cause loss of activity of the isoprenaline solution.

PHENYLEPHRINE HYDROCHLORIDE is a synthetic sympathomimetic amine which has a chemical structure similar to that of adrenaline. Compared with the others it has less effect on the myocardium, but it retains a pressor effect somewhat weaker than that of noradrenaline; and central nervous system stimulation is minimal. It is mainly used in diseases of the respiratory tract as a spray to produce vasoconstriction in the nasal mucosa; and in bronchial asthma it may be given as a 1 per cent solution in a nebuliser.

THEOPHYLLINE and its derivatives have many varied and important actions (pp. 41, 175), but none is more important clinically than that of Aminophylline (Theophylline with Ethylenediamine) giving immediate relief in nearly all cases of acute asthma

even when the paroxysm has failed to respond to adrenaline. It is much more difficult to assess the value of theophylline derivatives when they are given orally in chronic asthma: the response is likely to depend on the blood level obtained. These drugs cause gastric irritation and this has naturally limited the amount that can be given by mouth; but new preparations have been introduced and these are sometimes better tolerated. In addition to relaxation of bronchial muscle, theophylline stimulates the respiratory centre, both in normal subjects and when the respiratory centre is depressed. Thus aminophylline abolishes Cheyne-Stokes respiration when it is given intravenously. Other actions indirectly assist respiration: in congestive cardiac failure aminophylline produces a significant increase in cardiac output by direct stimulation of heart muscle; it is also diuretic and may be used as an adjuvant to mersalyl. Although appreciable blood levels may persist up to twelve hours the phase of therapeutic activity is confined to the times when concentration is at a peak; administration intravenously gives conspicuously better results than those obtained from intramuscular injection, and even when the drug is delivered direct into the blood stream the action is transient.

In acute asthma aminophylline is the preparation of choice: it is more soluble and more rapid in action than theophylline alone. It must be given slowly intravenously otherwise it may cause hypotensive effects. The usual dose is 0.25 G. The side-effects which may arise are syncopal in nature, but it must be emphasised that they are rare if the injection is given slowly—taking not less than one minute to empty the syringe gradually. Alternatively 0.5 G. may be given intramuscularly, but this causes pain at the site of injection and the discomfort may last for some hours. Aminophylline by mouth, 0.2–0.6 G., is seldom tolerated for long because the irritant effect in the stomach results in nausea. Attempts have been made to overcome this difficulty by dispensing aminophylline as a tablet with dried aluminium hydroxide gel. Choline theophyllinate is another preparation which has been introduced with the claim that it is more stable and therefore less irritant to the stomach—yet not so stable that it is not satisfactorily absorbed. In patients who derive therapeutic benefit from the oral administration of aminophylline, this prep-

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aration is worthy of trial, but the possibility remains that the individual patient will develop symptoms of gastric irritation. The dose is 100–200 mg. 4-hourly.

### DRUGS USED EMPIRICALLY

The introduction of *Corticotrophin* and *Cortisone* and its derivatives has been a major advance in the management of asthma. They can be life-saving in status asthmaticus when standard treatment with spasmolytic drugs has failed, and very impressive results are often seen even when patients are desperately ill. Unequivocal benefits of this kind are gratifying and also serve to emphasise our ignorance of the mode of action of these drugs in this condition. The most likely explanation is that the anti-inflammatory effect of the corticosteroids causes the congested and œdematous mucosa of the respiratory tract to return to its normal state. If this is so, it is clear that the therapeutic approach to the relief of asthma depends to an important extent on the state of the tissues of the respiratory tract when the patient is first seen, and therefore on the duration of the paroxysm. At the *start* of the paroxysm, *bronchiolar spasm* can usually be relieved if adrenaline is used promptly. If this is not done, mucosal swelling causes obstruction; patchy collapse and infection supervene—conditions which are scarcely affected by adrenaline and other spasmolytics, but which may be amenable to the effect of the corticosteroids. Excellent results are also seen in asthma which is known to be primarily allergic in origin, and this suggests that the corticosteroids are exerting their recognised action in modifying a hypersensitivity state—though in ways that are still far from clear.

The corticosteroids have only a suppressive action; asthma tends to relapse if the treatment is stopped too soon, or if the dose is cut too rapidly.

Status asthmaticus responds to standard treatment (adrenaline, aminophylline or isoprenaline) in the majority of instances, and unless the patient is exceptionally ill this should be tried for the first twenty-four hours. If the response is unsatisfactory cortisone is also given in the hope that a short course of this treatment will suffice: 300 mg. is given on the first day, then decreased by 25 mg.



daily, giving a total course of twelve days treatment. In a short course of this kind side-effects (p. 375) are not likely to occur but they must be kept in mind. When necessary, a course of therapy can usually be repeated without loss in effect. Cortisone seldom fails to give some relief, but in the more resistant attacks there may be a place for using corticotrophin instead. The rationale for this is that ACTH may release some more effective, but as yet unidentified, natural steroid from the adrenal glands.

Cortisone is of less value in chronic asthma, especially when it occurs in association with chronic bronchitis; but even here it can be of considerable help in exacerbations inadequately controlled by standard treatment (ephedrine, isoprenaline, or oral theophylline derivatives). Cortisone is given for three or four days at a time, for example, 300 mg., 200 mg., 100 mg., then 50 mg. or less per day. Also, even if cortisone gives incomplete relief, it is sometimes justifiable to prescribe it in small doses for prolonged periods, if this enables the patient to return to work or if it decreases the degree of disability significantly. This incurs a much greater risk of side-effects, such as atrophy of the adrenal glands, osteoporosis, reactivation of latent tuberculosis, or increased coagulability of the blood; and patients should be kept under regular supervision as the best insurance against serious mishaps. During prolonged courses corticotrophin, or corticotrophin gel, 20 units intramuscularly, is often given on every fourteenth day of treatment instead of cortisone, to try to preserve some adrenal function. Potassium Chloride 1-4 G. daily, orally, may be given to make good loss of potassium which may be excreted in the urine.

PREDNISONE (*deltacortisone*) and *Prednisolone* (*deltahydrocortisone*) are tending to replace cortisone for therapeutic purposes, as they are less likely to cause sodium retention and electrolyte imbalance, although more prone to cause gastric complications. For acute asthmatic attacks 5-10 mg. four times a day should be given initially, and an average maintenance dose in chronic asthma may be as little as 5 mg. twice daily. Occasionally these (or newer derivatives) will relieve asthma which is not responding satisfactorily to cortisone.

## DRUGS ACTING ON THE RESPIRATORY SYSTEM

**HYDROCORTISONE** is sometimes given by inhalation, in an attempt to achieve the same improvement from relatively small amounts deposited locally in the bronchi as are obtained from larger quantities given systematically. It is inhaled through the nostril with a hand-insufflator as a powder with a particle size of 5 microns; a half capsule is given at a time—each capsule containing 15 mg. of Hydrocortisone Acetate in 85 mg. of lactose powder. Excessive secretion in the respiratory tract reduces the efficiency of the inhalation.

## OXYGEN AND CARBON DIOXIDE

### OXYGEN

An adequate supply of oxygen is essential for the maintenance of life. The demand for oxygen is proportional to the activity of the organism: a great deal is needed during vigorous exercise and relatively little during sleep and by animals that hibernate; and oxygen consumption can be reduced artificially both in man and in animals by special techniques of cooling the body in the course of general anaesthesia. The physiological processes of respiration comprise the transport of oxygen from the external air via the lungs and blood stream to the tissue cells, the utilisation of oxygen in these cells, and the removal of carbon dioxide to the external air. Control over respiration is exerted mainly by the respiratory centre in the medulla: this is extremely sensitive to changes in the carbon dioxide tension of the blood, but less so to changes in oxygen tension. In addition the centre is influenced by reflex nervous impulses, by the *pH* of the blood, by cortical control, by poisons, by changes in the blood pressure, by fluctuations in the body temperature and in the temperature of the animal's environment. A reduced oxygen tension of the blood is a strong stimulus to the carotid and aortic chemoreceptors, which are much less sensitive to slight fluctuations of carbon dioxide tension.

If the supply of oxygen to the tissues is inadequate the condition is described as anoxia or hypoxia. This state may arise in a variety of circumstances, and several of these may exist simultaneously in clinical conditions such as congestive cardiac failure

—where there is both peripheral stasis and pulmonary œdema.

The term *anoxic anoxia* implies inadequate oxygenation of the blood leaving the lungs: it occurs at high altitudes because there is a lower partial pressure of oxygen, in patients with extensive pulmonary disease and consequent deficient alveolar ventilation, and in conditions where venous blood by-passes pulmonary tissue which is adequately ventilated, e.g. extensive pulmonary consolidation and some forms of congenital heart disease.

By *anæmic anoxia* is meant inadequate oxygen-carrying capacity of the blood such as may occur in severe anæmia, or where there is conversion of hæmoglobin to an abnormal type of pigment incapable of carrying oxygen.

*Stagnant anoxia* is the result of excessive reduction of oxy-hæmoglobin in the peripheral tissues as a result of disease of the peripheral circulatory system.

*Histotoxic anoxia* is rare, and is characterised by interruption of oxygen supply and utilisation in the cells of the peripheral tissues, as, for example, in cyanide poisoning.

Therapeutic administration of oxygen will clearly be of greatest value in those cases of anoxic anoxia where the lung tissue remains normal—for example at high altitudes, but it is also beneficial in diseases characterised by impaired diffusion as it raises the partial pressure of oxygen in the alveolar air.

Anoxic anoxia, if untreated, results in tachycardia and an increase in rate and depth of respiration from stimulation of the carotid chemoreceptors. Breathing appears to be embarrassed (clinical dyspnœa) when the respiratory minute volume exceeds about 50 per cent of the maximum breathing capacity; and this stage is reached much earlier by patients with extensive lung disease. Progressive anoxia leads to impairment of higher mental functions, analgesia, coma and finally respiratory failure and cessation of circulation.

The inhalation of pure oxygen by the normal subject can lead to only minimal increase in the uptake of oxygen by hæmoglobin which is near-saturated at the partial pressure of oxygen in normal alveolar air. The small quantity of oxygen dissolved in the plasma increases in direct proportion to the rise in partial pressure in the alveoli. The overall increase in oxygen content of arterial blood

## DRUGS ACTING ON THE RESPIRATORY SYSTEM

is about 10 per cent, but in the normal person there is also a 10 per cent increase in oxygen saturation of the venous blood. As the partial pressure of nitrogen in the alveolar air falls, nitrogen is rapidly eliminated on expiration. Other clinical effects noted on administration of pure oxygen are first a transient diminution and then an increase in respiratory minute volume, a decrease in cardiac rate, and peripheral vasoconstriction.

If the arterial blood is being only partially oxygenated a great increase in oxygen content may, of course, be possible.

*Toxic Effects.* The prolonged inhalation of increased oxygen concentrations, even at atmospheric pressure, may lead to certain toxic effects. Irritation of the respiratory passages, with increasing retrosternal discomfort, is common; it is thought that this is due to bronchial œdema, pulmonary œdema and patchy collapse. Fatigue, paræsthesiæ, anorexia and vomiting may develop. In premature infants high concentrations of oxygen are now known to lead to retrolental fibroplasia, perhaps with permanent blindness: on exposure to increased blood oxygen concentration the immature retinal vessels undergo obliteration.

During the administration of oxygen under *increased pressure* (as in diving) more dangerous symptoms arise from involvement of the central nervous system. Nausea, vertigo, and lack of concentration may soon give place to excitement and to epileptiform convulsions of grand mal type. It is commonly suggested that these features result from a toxic effect of high oxygen concentration on the enzyme systems of the pyruvic acid metabolic pathway.

In anoxic states the administration of oxygen may result in sudden apnœa, as the chemoreceptor stimulus to maintain respiration has been suppressed. In such circumstances the risk of death or tissue damage from anoxia means that oxygen therapy must be continued, if necessary by the use of controlled or artificial methods of respiration, until medullary control is re-established.

*Preparations.* Compressed Oxygen is dispensed in metal cylinders, distinguished by being painted black with white shoulders. Small, portable cylinders are available for domiciliary

use; and in many hospital wards a piped supply of oxygen is delivered from a central store (usually of liquid oxygen) to the individual bed.

**METHODS OF ADMINISTRATION.** In clinical practice, oxygen is usually inhaled at atmospheric pressure. A reducing valve is fitted on the cylinders and delivers oxygen to a flowmeter. Unless the latter is of the wash-bottle type, the oxygen should also be passed through water to prevent the irritant effect of the dry gas. Administration may then be by nasal catheters (for example, the Tudor-Edwards spectacle frame), face mask or oxygen tent. The expendable type of polythene mask is especially suitable. The tent has minor disadvantages in being cumbersome and tending to overheat the patient, but it is often life-saving. By catheter or mask a flow of 2-4 litres per minute will maintain about 50 per cent oxygen in the inspired air, and higher concentrations can be achieved with a well-fitted mask or in the tent. In view of the possibility of explosion, smoking should be strictly forbidden near oxygen supplies. Oxygen *under pressure* is rarely used clinically, but at high altitudes it is essential in order to maintain efficient oxygenation.

**THERAPEUTIC USES.** The main therapeutic uses have been mentioned above. In respiratory diseases oxygen is of the greatest value in acute illness, or acute exacerbations of chronic disabilities. In chronic respiratory disease with anoxia, there is often retention of carbon dioxide, and the administration of oxygen may result in diminished respiration, and aggravation of carbon dioxide retention. However, the dangers of anoxia usually outweigh the risk of inducing "carbon dioxide narcosis". Oxygen therapy is therefore not withheld from patients with this form of chronic respiratory failure, but it should be given intermittently and in *small amounts* to establish the degree of tolerance. Oxygen is of less value in circulatory disorders unless these are associated with pulmonary oedema. In patients suffering from chronic pulmonary disease with recurring episodes of anoxia, the phenomenon of *dependence* on oxygen therapy is occasionally seen. This condition is largely psychological in origin: the patient

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requires firm reassurance from the physician that supplementary oxygen is no longer needed.

In carbon monoxide poisoning, oxygen is given in combination with carbon dioxide. The  $\text{CO}_2$  stimulates the failing respiratory centre; inhalation of oxygen is intended to ensure that the maximum oxygenation of the tissues is achieved by oxyhæmoglobin and full saturation of the blood plasma. It must be emphasised that hæmoglobin which has been converted to *carboxy-hæmoglobin* is not available for transportation of oxygen; its conversion to oxyhæmoglobin proceeds very slowly and is not accelerated to an important degree by oxygen therapy. In cases of carbon monoxide poisoning the immediate treatment aims at tiding the patient over a phase of anoxia attributable to this "immobilisation" of hæmoglobin.

### CARBON DIOXIDE

Though carbon dioxide is of profound importance in the physiological control of respiration, therapeutically it is less important than oxygen. The carbon dioxide tension of the blood is maintained within narrow limits, most of the gas being transported in the combined form—as bicarbonate, buffered by phosphate, hæmoglobin and plasma protein.

*Chemistry.* Carbon dioxide is an odourless, colourless gas which is denser than air. At low temperatures the gas solidifies to form "carbon dioxide snow".

**PHARMACOLOGICAL ACTIONS.** The most obvious effect of carbon dioxide is on respiration. When atmospheric air which normally contains 0.05 per cent carbon dioxide is replaced by as little as 2 per cent carbon dioxide the rate and depth of respiration are noticeably increased. This effect is due mainly to specific stimulation of the respiratory centre, but there is also reflex stimulation from carotid chemoreceptors. The increase in minute volume is proportional to the increase in carbon dioxide concentration, until the maximum effect is achieved at 10 per cent. With higher concentrations there is progressive depression of body functions as a whole, with ataxia, respiratory failure and death.

With certain exceptions the patient suffering from severe anoxia already has a considerable degree of carbon dioxide retention, and if respiratory failure has supervened the therapeutic administration of carbon dioxide in an attempt to produce respiratory stimulation may aggravate the situation.

Inhalation of increased concentrations of carbon dioxide leads to an increase in heart rate, an increased force of cardiac contraction and a rise in blood pressure. There is a selective increase in cerebral circulation, with vasoconstriction in other vascular beds. Headache is common; mental depression and anæsthesia may also occur.

Local actions of carbon dioxide which are useful in clinical practice include the use of carbon dioxide snow to produce localised destruction of tissues—usually a skin lesion—by freezing, and the use of aerated water as a “flavouring” agent or gastric stimulant and carminative.

*Toxic Effects.* The inhalation of carbon dioxide mixtures produces toxic effects which have been mentioned. With the usual clinical concentration of 5–7 per cent in oxygen, intense dyspnœa may occur, and headache usually develops if administration is prolonged. Faintness and dizziness are more common on withdrawing the gas, because the blood-pressure falls. Palpitation, paræsthesiæ and mild mental confusion are commonly noted. The inhalation of 10 per cent carbon dioxide mixtures may produce coma within 15 minutes.

*Preparations.* Carbon Dioxide is made available in compressed form in metal cylinders, the concentration varying from 5–10 per cent in oxygen. Cylinders of pure carbon dioxide are painted grey; those containing oxygen and carbon dioxide are black with grey and white quartering on neck and shoulders. Carbon dioxide snow is made by allowing the rapid escape of compressed gas from the cylinder; it is collected in a bag of suitable fabric and compressed in a mould to form a stick of suitable size.

*Methods of Administration.* Carbon dioxide is administered in 5–10 per cent concentration in oxygen by means of a well-fitting

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face mask. Carbon dioxide snow is applied, with pressure, to tissue to be frozen and destroyed.

**THERAPEUTIC USES.** The main clinical use of inhalation of 5 per cent carbon dioxide is to increase the rate and depth of respiration where there is respiratory depression. By this means noxious gases are expelled from the lungs and atelectasis (collapse of lung tissue) prevented. However, in most cases of asphyxia there is already carbon dioxide retention and, as explained above, the inhalation of an increased concentration of carbon dioxide may be dangerous. The exception to this rule is in carbon monoxide poisoning where there has been no impairment of carbon dioxide excretion, and no carbon dioxide retention; in this condition the inhalation of 5 per cent carbon dioxide in oxygen is recommended. Carbon dioxide inhalation for a short period during recovery from a general anæsthetic hastens the elimination of anæsthetic gases and reduces the risk of pulmonary collapse. Carbon dioxide inhalations often terminate attacks of hiccough, and may arrest the minor seizures of petit mal epilepsy—though this is a matter of interest rather than one of therapeutic importance. Carbon dioxide snow is applied to destroy, by freezing, overgrown tissues such as warts and nævi. In the succeeding days the treated part is inflamed, and scar formation occurs as it is nearly always necessary in such cases to destroy a small part of the cutis vera.



## CHAPTER 12

# PHARMACOLOGY OF THE ENDOCRINE GLANDS

THE secretions of the endocrine glands play an important part in the regulation of metabolic processes. This is their major role, but some of them—such as the trophic pituitary hormones—control the activity of other endocrine glands; others have a special function to perform, for example prolactin influences lactation, and the sex hormones affect the organs of reproduction. In health, self-adjusting mechanisms exist whereby increased need for a hormone is met by an increased output. This is well seen in those endocrines controlled by the anterior pituitary lobe. Thus a falling blood level of the adrenal cortical hormone, hydrocortisone, calls forth an increased secretion of adrenocorticotrophic hormone (ACTH) which stimulates the production of hydrocortisone from the adrenal cortex. *Per contra*, the administration of hydrocortisone reduces the output of ACTH. In the same way administration of oestrogens diminish the secretion of pituitary gonadotrophins; in addition, however, they can inhibit secretion of prolactin and growth hormone. Such physiological responses in the endocrine system are sometimes made use of therapeutically as will be described later in this chapter.

The common type of hormone disorder is deficient secretion from one of the glands, and treatment consists of supplying either the natural hormone obtained from animals or a synthetic equivalent. Overactivity of an endocrine gland is commonly treated surgically or by radiation, but for the common disease thyrotoxicosis, important drugs are available which diminish the synthesis of the thyroid hormone.

Certain hormones are used outside their natural field of therapeutics on account of some special action. Cortisone and its analogues, when given in large doses, can be used to suppress the inflammatory reaction in certain diseases. Insulin is occasionally

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used to increase appetite in patients suffering from anorexia when this is a symptom of mental disturbance.

Chemically the hormones are heterogeneous: the parathyroid hormone is thought to be a protein; insulin and all the pituitary hormones are polypeptides, and the thyroid hormones are iodinated amino acids. The sex hormones and adrenal cortical hormones are steroids and the adrenal medullary hormones are catechols derived from the amino acid tyrosine.

### THYROID

The thyroid hormones, thyroxine (tetra-iodothyronine) and tri-iodothyronine are formed by the thyroid cells from iodine and tyrosine. They are stored within the molecule of thyroglobulin in the colloid and are released under the action of the thyrotrophic hormone of the pituitary (TSH) into the blood where they circulate attached to a globulin (protein-bound iodine, PBI). Thyroxine is present both in the gland and the blood in greater amounts than tri-iodothyronine. It is thought that in the tissues thyroxine loses an atom of iodine to become tri-iodothyronine which may be the active hormonal agent.

In health the body uses 0.1-0.4 mg. of thyroxine per day which is equivalent to 60-240 mg. of thyroid. The official dose of thyroid is 30-240 mg. Thyroid or dry thyroid is a cream-coloured powder made from the thyroid glands of animals. It consists essentially of thyroglobulin and is standardised chemically to contain 0.1 per cent iodine bound to thyroxine. It is taken orally as a tablet; the official tablet contains 30 mg. but tablets containing smaller and greater amounts of thyroid are available. Lævothyroxine sodium requires no standardisation as it is chemically pure. It is available as tablets containing 0.05 mg. and 0.10 mg. Tri-iodothyronine is officially known as Liothyronine.

Thyroid is well absorbed from the bowel and is distributed to all tissues. Its fate in the body is not fully known. Both the liver and the kidney are concerned with the degradation of thyroid hormones and, in animals, conjugates of thyroxine and tri-iodothyronine are excreted into the bowel in the bile. In man the iodide from the degraded hormone is taken up once again by the thyroid cells, or is excreted in the urine.

## DILLING'S CLINICAL PHARMACOLOGY

**ACTION OF THYROID.** Thyroid hormone is concerned with oxygen consumption and thus with the functional activity of all cells in the body. How its action is brought about within the cell is not known. When given to a normal person thyroid depresses the output of TSH and in consequence the secretion of endogenous thyroid hormone is diminished. In doses up to 120 mg. thyroid produces no demonstrable clinical effect in the normal person, since the output of hormone from the gland has been correspondingly decreased. There is no justification for giving thyroid to patients who do not show the clinical signs of hypothyroidism. When a daily dose of 180 mg. or more is given some manifestations of overdosage appear, but the normal person is relatively resistant to the action of administered thyroid in contrast to the patient with myxœdema.

*Action of Thyroid in Hypothyroidism.* When there is deficiency of thyroid secretion (cretinism in the infant, myxœdema in the juvenile and adult) the general depression of metabolic activity is shown as a slowing up of all the functions of the body. In addition the tissues become infiltrated with a mucinoid material which further impairs the function of the organs. In the infant and the child the thyroid hormone plays an important part in growth and development. When it is lacking, in addition to the general features of hypothyroidism, there is stunting of growth and the development of the brain and skeleton is retarded. Puberty may also be delayed.

When thyroid or thyroxine is given to a patient suffering from thyroid deficiency the characteristic actions appear slowly. Increased consumption of oxygen (indicated by BMR readings) is only demonstrable after a latent period of 1-2 days and the maximum effect of a constant daily dose is not obtained for 7-10 days. Likewise if thyroid is stopped the metabolic effects subside slowly over several weeks. Thyroxine and thyroid have cumulative effects: the dose must therefore be increased cautiously and at intervals of not less than 7 days.

In myxœdema, after the latent period, a diuresis occurs as the water locked in the mucinoid material is liberated, and as renal blood flow increases. Nitrogenous waste products from the combustion of stored protein also contribute to the diuresis. The rate

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of absorption of sugars from the bowel is increased and the utilisation of carbohydrate by the tissues is accelerated. The removal of the mucinoid material from the tissues causes the patient to lose weight. The puffiness of the face disappears, the voice becomes less leathery, and hearing is improved. The increased heat production makes the patient less sensitive to cold. Both mentally and physically he becomes more alert. The rough scaly skin and the lustreless hair take longer to improve. The heart rate is increased, the heart size diminishes and the low complexes shown on the electrocardiogram are augmented.

Dry thyroid is a potent preparation and myxœdematous patients are much more sensitive to it than are normal subjects. Frequently also the subthyroid patient has coronary atherosclerosis and an undue increase in heart rate may induce anginal pain. Further, the myocardium is frequently affected by the myxœdematous process and recovers slowly under thyroid medication. Large initial doses, by increasing metabolism and heart rate too quickly may place too great a load on the heart and failure results. When the heart is obviously affected, a dose of 10–15 mg. should be given daily and cautiously increased. Otherwise an initial dose of 30–60 mg. should be given once per day and increments of 15–30 mg. made every two weeks until 180 mg. are being given or until symptoms of overdosage appear. Regular treatment is needed for the rest of the patient's life.

For the cretinous infant an initial dose of 6 mg. should be given and increased gradually until evidence of mild overdosage appears, when the dose is reduced slightly. The maximum tolerated dose is required to ensure full growth and normal development. Early recognition and adequate therapy will result in a normal child. The treatment is for life.

The use of thyroid in menstrual disorders is irrational and ineffective save when menorrhagia is part of the picture of myxœdema. Thyroid and thyroxine have little value in the treatment of obesity.

Thyroid given in excessive doses causes a proportional increase in the metabolic rate and overstimulation of the heart and nervous system. The patient loses weight, and there is generalised sweating and flushing of the skin. Glycosuria may occur. The

pulse rate is rapid and the patient may complain of palpitation and anginal pain. Insomnia, increased excitability, overactivity and muscular weakness are other common symptoms. The pupils may be dilated and the eyes appear to be staring because there is slight retraction of the upper lids. These ocular signs and the tachycardia are attributable to the more sensitive state of the sympathetic nervous system induced by an excess of thyroxine. When any of these symptoms and signs appear, thyroid medication should be stopped for several days, and when it is resumed smaller doses should be given.

*L-Thyroxine Sodium* is a cream-coloured powder; 0.1 mg. is approximately equal in therapeutic activity to 60 mg. of thyroid. As the potency of dry thyroid is inconstant, many clinicians prefer to use *l*-thyroxine sodium in the treatment of patients with hypothyroidism.

*Liothyronine* (tri-iodothyronine) has actions identical with those of thyroxine. It is, however, much more potent and its action begins immediately on absorption. Patients exhibiting hypothyroidism who are treated with liothyronine sodium relapse very quickly when the preparation is withdrawn. It has no advantage over thyroid and thyroxine for the treatment of thyroid-deficiency states. It may be used as a test for thyrotoxicosis in association with  $^{131}\text{I}$  uptake tests. Treatment for one week with 100 micrograms daily of liothyronine sodium will suppress the uptake of radio-iodine by the normal thyroid gland but will fail to do so if the gland is thyrotoxic.

#### ANTITHYROID DRUGS

Two different types of treatment are available for thyrotoxicosis: (1) procedures such as thyroidectomy and irradiation by radio-active iodine both of which remove a large part of the over-active goitre; and (2) drugs which reduce the rate of formation of the thyroid hormone (the antithyroid agents) or diminish the quantity of hormone released into the circulation.

A brief consideration of the biosynthesis of the thyroid hormone is necessary to elucidate the mode of action of the drugs used in thyrotoxicosis. The two major stages in the formation of

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the thyroid hormone are: (1) the withdrawal of iodide from the blood by the thyroid cells; and (2) the organic binding of iodine to tyrosine. The first stage in the latter process involves the oxidation of iodide to iodine by enzymes. Following the iodination of tyrosine a series of reactions occur culminating in the formation of thyroxine and tri-iodothyronine in the storage protein, thyroglobulin. The release of the hormones into the circulation is brought about by the action of the thyroid protease on thyroglobulin. All the phases of synthesis and release are governed by the pituitary hormone TSH, the secretion of which is controlled by the level of circulating thyroid hormones. When the hormone level is low from any cause, increased TSH secretion occurs and if sustained it will cause hyperplasia of thyroid tissue—that is, a *goitre* develops.

The drugs which cause a reduction in thyroid secretion may be classified as follows:

(a) Those which prevent the thyroid cell from withdrawing iodine from the blood, such as the thiocyanates and perchlorates.

(b) Agents which block the organic binding of iodine to tyrosine, e.g. thiouracil and its derivatives. Other drugs not used for their antithyroid action such as *p*-aminosalicylic acid, resorcinol and certain sulphonamides may show the same effect as a side-action.

The drugs in both groups are sometimes called “goitrogens”. One effect which they have in common is to reduce the amount of thyroxine in circulation. This is the signal for an increase in the secretion of thyroid-stimulating hormone. An excess of TSH causes hypertrophy of the thyroid; and the goitrous gland may or may not provide the additional secretion of thyroxine which is needed for normal metabolism.

(c) Iodine—which temporarily reduces the rate of release of the thyroid hormone from the gland.

In thyrotoxicosis, iodine, the thiouracil derivatives, the perchlorates and radio-active iodine are the drugs used therapeutically: other preparations mentioned above are of pharmacological interest only.

**IODINE.** Paradoxically iodine—one of the raw materials for the biosynthesis of thyroxine—is able, in thyrotoxicosis, to

promote storage of the thyroid hormone and slow the rate of release into the blood. It is not known how this is accomplished, but the effect is compatible with an inhibition or a neutralisation of TSH. The goitre becomes smaller, firmer and less vascular. Histologically the overactive acini lined with tall columnar epithelium and containing scanty colloid pass into the resting phase in which the acini are full of colloid and the lining cells are flat or cuboidal. The effect, however, is incomplete, some of the acini failing to revert to the resting stage. Clinically there is a conspicuous improvement in the condition of the thyrotoxic patient. Within a few days the patient becomes more composed and less excitable; the pulse rate falls, sweating is less troublesome, and BMR readings begin to show a downward trend. The maximum benefit is apparent in 10-14 days, but the remission is never complete: some mild symptoms of thyroid overactivity persist. After 2-3 weeks the clinical features reappear despite continued administration of iodine. This form of therapy is therefore of no value for the prolonged medical treatment of thyrotoxicosis: it is employed only as a preparation for thyroidectomy. Although it may be given as the sole antithyroid drug before operation, it is commonly used following a course of a thiouracil derivative given to reduce synthesis of the thyroid hormone. Iodine given in this way reduces the vascularity and friability of the goitre and makes thyroidectomy a less difficult procedure.

A suitable preparation is Potassium Iodide 60 mg. three times daily for 10-14 days. Alternatively Lugol's watery solution of iodine (5 per cent iodine in 10 per cent solution of potassium iodide) is given in 0.3 ml. doses thrice daily. "Lugol's Iodine" has no special therapeutic advantages. Its use is largely a matter of tradition, and it is readily available. To obtain a satisfactory result from such a course of iodine, no iodine or iodine-containing medicine should have been taken in the previous month.

**THIOURACIL GROUP.** The thiouracil group of antithyroid drugs comprises thiouracil and its methyl and propyl derivatives; and methimazole and carbimazole ("Neomercazole"). The original drug, thiourea, was abandoned when the more active

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and less toxic thiouracil became available, and at the present time only methylthiouracil and carbimazole are commonly used.

All these drugs act in the same way: they diminish the formation of the thyroid hormones by preventing the attachment of iodine to tyrosine. How this is brought about is not known. They are all strong reducing agents and it seems likely that when iodide is oxidised to iodine they promptly reduce iodine—forming iodide again, so that it is not available for attachment to tyrosine. They do not interfere with the peripheral effects of thyroxine: this preparation still produces its typical actions when given to an animal which is already under treatment with a thiouracil drug.

These drugs are readily absorbed from the intestinal tract. Only a small fraction of the dose is destroyed before absorption. They are distributed to all tissues and body fluids, pass through the placenta and are secreted in the milk. The highest concentrations of thiouracil are found in the bone marrow, white blood cells, and in the thyroid and pituitary glands. More than half of the administered dose is destroyed in the tissues and a further quarter is excreted in the urine, largely in a combined form.

The antithyroid drugs vary in their potency and in their clinical toxicity. The most potent and least toxic is carbimazole, and this is the drug of choice. Methylthiouracil and propylthiouracil have approximately one-tenth the potency of carbimazole and have a slightly higher incidence of serious side-effects.

*Action in Thyrotoxicosis.* Since the thiouracil group of drugs act by reducing the rate of synthesis of thyroxine, no clinical effect is demonstrable until the hormone already formed and stored in the gland is utilised. There is thus a latent period of 1-2 weeks before clinical improvement begins. Excitability and restlessness then diminish, sweating and flushing become less and the weight begins to increase. The BMR and the pulse rate start falling and within a period of 3-5 weeks most patients are in a euthyroid state. Tachycardia may be the last clinical feature to remit. When auricular fibrillation is present there is a 50 per cent chance that therapy will restore the rhythm to normal. Little change occurs in the size of the goitre, which tends to



become softer and more vascular. Exophthalmos is commonly unaffected; in a few it may increase, in others it may diminish.

The antithyroid drugs are taken orally as tablets. The Tablet of Carbimazole contains 5 mg. and the Tablet of Methylthiouracil 50 mg. The controlling dose to bring the patient to a "euthyroid state" is 30–60 mg. carbimazole given daily in divided doses, or 200–600 mg. methylthiouracil. When a satisfactory remission has been achieved the dosage is reduced to maintenance levels, 5–20 mg. daily for carbimazole and 50–200 mg. for methylthiouracil. For each patient the optimum maintenance dose has to be determined by trial and error. Overdosage is heralded by the appearance of symptoms and signs of mild myxœdema (sensitivity to cold, roughening of the skin, slowing of speech, etc.) and by an increase in size of the goitre. This last sign is brought about by thyroxine deficiency which calls forth an increased secretion of thyrotrophin (TSH) with resulting thyroid hyperplasia (p. 359).

*Toxic Effects.* All the thiouracil derivatives are liable to depress the bone marrow. Agranulocytosis, leucopenia, thrombocytopenia and pure red cell anæmia may be induced. The most important is agranulocytosis which calls for immediate cessation of the drug and the administration of penicillin. The incidence of blood dyscrasias is about 1 per cent with carbimazole and about 2 per cent with methylthiouracil. Drug fever and toxic hepatitis also call for stoppage of therapy. (Edema of the legs, lymph node enlargement, conjunctivitis and rashes of urticarial and maculopapular types have all been reported. Close observation is indicated of patients under prolonged medication with these drugs—and especially during the first 2 months.

These antithyroid preparations are used to treat the young patient with mild thyrotoxicosis. After therapy lasting for one year, about 50 per cent relapse when the drug is withdrawn. Thyroidectomy should then be considered or a further course of carbimazole. For older patients between the ages of 35 and 45 years thyroidectomy is the treatment of choice. A course of carbimazole is given to make the patient euthyroid and 10–14 days before operation iodine is given to reduce the vascularity of the goitre.

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For patients over 45 years radio-iodine is the treatment at present preferred by many physicians.

POTASSIUM PERCHLORATE which acts by blocking the uptake of iodide by the thyroid cells is a much less potent antithyroid substance than the thiouracils. Doses of 600–1,200 mg. are required daily and the response obtained is slow. It has the advantage of being cheap and virtually non-toxic. It may be used when continuance of medical treatment is warranted in a patient who has experienced a serious toxic effect from a thiouracil type of drug. The administration of iodine to a patient having perchlorate treatment annuls the effect completely.

RADIO-ACTIVE IODINE. Radio-active iodine is of value in the investigation of thyroid disorders and in the treatment of certain cases of thyrotoxicosis and thyroid cancer. The isotope most commonly used is  $^{131}\text{I}$  which is made in the atomic pile. It has a half-life of 8 days, and emits both *beta* and *gamma* rays. As the *beta* rays have ionising properties they destroy cells; but on account of their poor penetration (1–2 mm.) their destructive effect is local. *Beta* rays are not detectable by instruments outside the body, but *gamma* rays (which have little effect on cells) are readily picked up by electronic counters.

$^{131}\text{I}$  behaves like stable iodine. It is taken up by the thyroid cells, incorporated into the thyroid hormone and appears in the blood as radio-active protein-bound iodine ( $\text{PB}^{131}\text{I}$ ). The fraction not used by the thyroid is excreted in the urine over 24–48 hours.

Following a tracer dose of  $^{131}\text{I}$  it is possible by measuring the *gamma* radiation from the thyroid gland, to obtain an idea of the rate of uptake of iodine by the thyroid cells. In general an uptake of over 50 per cent of the tracer dose at 48 hours is regarded as evidence of overactivity of the thyroid gland. An uptake below 20 per cent points to a diagnosis of myxœdema. The poor uptake of  $^{131}\text{I}$  in myxœdema is reflected in the high proportion of the tracer dose to be found in the urine and the percentage excretion of the dose is a valuable and relatively simple means of detecting subthyroidism. The blood level of thyroid hormone tagged with  $^{131}\text{I}$  is also readily measured, and the value obtained 24 or 48

hours after a tracer dose is one of the best single tests for separating normal from thyrotoxic patients. These procedures require complicated and expensive equipment which is available only at special centres.

The *beta*-radiation from the small tracer doses of  $^{131}\text{I}$  used in diagnostic work is insufficient to affect thyroid cells. By giving much larger doses, the *beta*-radiation from  $^{131}\text{I}$  trapped and stored in the gland destroys the thyroid cells over a number of weeks. Since the range of *beta*-radiation is very limited the tissues outside the thyroid are not affected. This is the basis for the use of radio-active iodine in the treatment of thyrotoxicosis and thyroid cancer. The treatment is exceedingly simple: the patient takes a drink of water containing the tasteless radio-iodine. In thyrotoxicosis the aim is to reduce the amount of functioning thyroid tissue to normal and this can be accomplished after one therapeutic dose in a high proportion of cases. Symptomatic improvement begins in 2-3 weeks and the full effect is obtained in about 2 months. A phase of myxœdema may appear but in only a few is this permanent. Persistence of overactivity is treated by 1 or 2 further doses of  $^{131}\text{I}$  usually of smaller size than the first. Therapeutic radio-iodine is contra-indicated in pregnancy and in childhood. Since the risk of inducing delayed neoplastic change in the thyroid is not yet known, this form of treatment is generally reserved for thyrotoxic patients over the age of 45 years. It may also be given to patients who have relapsed after thyroidectomy, and to those in whom conventional therapeutic measures are hazardous.

Certain types of thyroid cancer respond to radio-iodine. The anaplastic type is untouched since the cell does not take up iodine. Other forms vary in their sensitivity and the response is better in those cases where the cancer cell will trap iodine. It is possible sometimes to increase the uptake of iodine by the primary growth and the secondary deposits by inducing myxœdema. Large and repeated doses of  $^{131}\text{I}$  are required over many months or years. Radio-iodine therapy does not dispense with the need for surgical removal of the primary growth if this is feasible.

## INSULIN

**INTRODUCTION.** A working knowledge of the effects of insulin presupposes an understanding of current concepts of metabolism, and especially of its hormonal control. The student has already covered this ground in his preclinical courses in physiology and biochemistry. Strictly speaking in the pharmacological approach to the action of insulin there is nothing to add to the physiologist's version of the subject. Certain aspects that are of special importance to the clinician are selected for emphasis. Details regarding the choice of preparation in relation to various clinical circumstances, the dietetic requirements of patients, and the management of complications arising in the course of diabetes are matters beyond the scope of this book: they receive detailed consideration in manuals of therapeutics and in special monographs.

Insulin is the principal hormone secreted by the pancreas. In the late 19th century it had been noted that removal of the animal pancreas produced a condition resembling the disease diabetes mellitus. However, it was not until 1921 that Banting and Best were able to produce from the pancreas an extract with a potent beneficial effect on the pancreatectomised animal. Insulin was tried in the therapy of human diabetes in 1922, with results that were clearly promising.

*Source.* Insulin is formed in the  $\beta$ -cells of the pancreas of mammals and fishes; though it has been synthesised (a major biochemical achievement), commercial production of insulin is by a process of extraction from animal pancreas and subsequent purification.

*Chemistry.* Insulin is a protein with a molecular weight of about 35,000. The molecule consists of polypeptide chains arranged in three groups.

**PHYSIOLOGY AND PHARMACOLOGY.** The most obvious action of insulin in both normal and diabetic persons is a lowering of the blood glucose level. Insulin permits the conversion of glucose into glucose-6-phosphate, the only form in which it can

be utilised for energy production, or stored as intracellular glycogen. This fall in blood glucose level has well-defined effects mediated by the autonomic nervous system, including increased gastric secretion and the effects of increased output of adrenaline. Hypoglycæmia is described in greater detail below. Strictly, insulin has no pharmacological actions, other than those which result directly or indirectly from the regulation of carbohydrate metabolism.

The disease diabetes mellitus results from insulin deficiency, due either to failure of pancreatic secretion, or because of a relative deficiency from the antagonistic effects of other substances—such as other hormones. In diabetes the utilisation and storage of glucose are impaired, but as the breakdown of glycogen and formation of glucose from fat and protein continue, hyperglycæmia, glycosuria, polyuria and thirst develop. In severe cases the breakdown of fat is accelerated with an overloading of the normal biochemical pathway for removal of ketone bodies. This state is known as diabetic ketosis, and if uncorrected may lead to coma and death.

**TOXICOLOGY.** Insulin itself is non-toxic but in overdosage it may produce serious effects. The most important consequence is hypoglycæmia—recognised from certain characteristic clinical features when there is a *rapid* fall in blood sugar. The symptoms and signs are those of adrenaline release and of cerebral anoxia. The latter is due to diminished oxygen uptake in the glucose-depleted cerebral cells and not to diminished cerebral blood flow or altered pulmonary oxygenation. The early clinical features of hypoglycæmia are a vague feeling of apprehension, hunger, nausea, and there is often tremor, giddiness and mental confusion (disorientation). Pallor of the skin and sweating are highly characteristic; the pulse-rate and blood pressure are raised, and the plantar response may be extensor. Coma, convulsions and death may ensue if correction of the low blood sugar is unduly delayed.

Local allergic reactions occur occasionally with injected insulin, more commonly with preparations containing foreign protein. Extensive atrophy of the subcutaneous fat at the site of insulin injection is a rare complication.

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*Resistance* to treatment (failure to respond normally) with insulin is occasionally a troublesome phenomenon—even when enormous doses are given. This is thought to be due to the formation of insulin antibody: fortunately it is self-limiting.

*Absorption, Fate and Excretion.* Insulin is digested if given orally, and is therefore inactive if given by this route. On subcutaneous injection of purified soluble insulin the hormone is rapidly absorbed and utilised. To prolong the action, methods of combining insulin with foreign protein material and metals such as zinc have been developed. The object is to retard absorption at the injection site. Details regarding these preparations are given below. The result of this pharmaceutical modification is to produce a “depot insulin” which in clinical use mimics closely the activity of normal pancreas, producing a more sustained effect than soluble insulin.

Insulin is not excreted; it is rapidly bound in the tissues, where some may be inactivated by an enzyme “insulinase”.

*Preparations and Dosage. Insulin Injection* (Soluble Insulin) is a clear solution of the purified hormone, marketed in strengths of 20, 40 or 80 Units per ml. When injected subcutaneously it is active within 30 minutes, reaches a peak in 3 hours, and lasts up to 12 hours. This form of insulin is preferred in the management of severe diabetes, especially when complicated by infection, ketosis, pregnancy or surgical operation. Soluble insulin is given twice daily or oftener.

The longer-acting preparations are marketed in strengths of 40 or 80 Units per ml. only and are as follows:

*Protamine Zinc Insulin Injection* (Protamine Zinc Insulin) is formed from the combination of insulin with a suitable protamine in the presence of zinc chloride. Its action is slow in onset (4–5 hours), is maximal in 15–18 hours, and may persist for over 36 hours. As the onset of the effects is slow it is usual to give a dose of soluble insulin simultaneously. This must not be given in the same syringe, otherwise much of the soluble insulin is converted into protamine zinc insulin.

*Globin Zinc Insulin Injection* (Globin Insulin) occupies an inter-

mediate place: it takes effect in 1-2 hours and its maximal action occurs in 12 hours. This preparation is less commonly used now.

Insulin Zinc Suspensions are produced from the interactions of zinc chloride with insulin in an acetate buffer solution. During this reaction variation in the pH and in other factors results in the separation of two fractions—the amorphous and the crystalline. These suspensions can be mixed in any suitable proportions.

*Insulin Zinc Suspension (Amorphous)* is of intermediate action ("semilente insulin"). This action, however, is of rapid onset (30 minutes), is maximal in 2 or 3 hours and lasts for 12 hours.

*Insulin Zinc Suspension (Crystalline)* produces a prolonged effect ("ultralente insulin"): its action appears in 1-2 hours, is maximal in 7-10 hours and lasts for 36 hours. The mixture most widely used is marketed as *Insulin Zinc Suspension* (IZS or "lente insulin"). This preparation begins to act within 1 hour and the effect lasts for 24 hours. In practice it is found possible to provide therapeutic control in many patients by giving them a single daily dose of IZS.

Preparations of insulin are standardised by biological assay using the rabbit or mouse as the test animal, and comparing the effect against a standard preparation of known potency.

*Routes of Administration.* Insulin is injected by the subcutaneous route, but in emergency soluble insulin may be given intravenously. Although insulin given direct into the bloodstream is immediately available, it is also destroyed much more rapidly in these circumstances. Allowance should be made for this by giving *larger* doses intravenously than would normally be given subcutaneously. In treating a patient, however, it is likely that both routes would be used and that intravenous injections would be discontinued when it was apparent that soluble insulin given subcutaneously had begun to act. There is no fixed "dose": the amount is adjusted to the needs of the patient. Often the requirement in diabetes is between 10 and 100 Units daily, but a few patients need even larger doses.

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Insulin is occasionally used for other purposes: for example, in the treatment of schizophrenia, coma may be induced therapeutically by means of insulin; it may also be injected to stimulate appetite in intractable cases of anorexia, and it is used in certain diagnostic procedures (insulin test meal, insulin sensitivity test).

**ORAL HYPOGLYCÆMIC AGENTS.** A group of drugs recently introduced have a hypoglycæmic action when given by mouth, and these have already proved valuable in the treatment of selected cases of diabetes mellitus.

These substances are all arylsulphonylureas. Some have a typical sulphonamide structure with an amino group attached to the benzene ring; others lack this configuration and are without the antibacterial activity and toxic effects of sulphonamides. The effect of these drugs is believed to result mainly from stimulation of insulin production in the pancreas, and possibly also from promoting glycogen deposition in the liver.

*Carbutamide* (BZ55) was the first arylsulphonylurea compound to be tried in the treatment of diabetes. It has a hypoglycæmic action, and it also shows antibacterial activity. However, it has been found to produce frequent toxic reactions, notably skin rashes, thrombocytopenic purpura and leucopenia.

*Tolbutamide* lacks the characteristic sulphonamide grouping, and has no bacteriostatic action. Toxic effects are infrequent; a soluble carboxylated derivative is excreted in the urine. Tolbutamide is used in the treatment of a small minority of diabetics—those who are middle-aged or elderly, in whom the disease is mild, and who show no tendency to ketosis. The usual dose at first is 1 G. three times daily, later reduced to 0.5 G. twice or thrice daily.

*Chlorpropamide* is a newly introduced hypoglycæmic agent. The only advantage over tolbutamide lies in its long duration of action: a single dose of 0.2-0.5 G. daily produces a hypoglycæmic action lasting 24 hours. This is due to slow renal excretion. Experience of chlorpropamide does not yet warrant drawing firm conclusions regarding its value, but toxic effects on the blood and liver have been noted. The hepatic damage resembles that which has been reported after chlorpromazine therapy; the jaundice is predominantly obstructive in type.



## ADRENAL STEROIDS

The principal metabolic function of the adrenal steroids, or corticoids, is to maintain stability of the internal environment. This is accomplished by the control they exercise over electrolyte, water, carbohydrate, protein and fat metabolism. They probably also have some fundamental action on all cells enabling them to adapt to changes in the internal environment. The mechanism of action at the cellular level is unknown.

The adrenal steroids are classified on a structural and functional basis as (i) mineralocorticoids which primarily affect electrolyte and fluid balance, (ii) glucocorticoids which influence carbohydrate and protein metabolism, and (iii) adrenal androgens which in addition to their virilising activity promote protein anabolism.

ALDOSTERONE, the natural mineralocorticoid, is synthesised in the zona glomerulosa. It is secreted when sodium loss or potassium retention occurs and when the extracellular fluid volume falls. Corticotrophin augments aldosterone secretion but only mildly and transitorily. It is not available for clinical use and the semisynthetic steroid, deoxycortone, is used instead.

DEOXYCORTONE has all the actions of aldosterone but has only about one-twenty-fifth of its potency.

Aldosterone and deoxycortone act on the renal tubule to cause retention of sodium and excretion of potassium. They also reduce the sodium content of the saliva, sweat and intestinal secretions. The net result of this retention of sodium is expansion of the extracellular fluid volume. This is the essential action of deoxycortone in adrenal insufficiency. The blood volume and blood pressure increase and the weight rises; and potassium is excreted. With excessive doses oedema and hypertension appear and the subnormal level of serum potassium may result in muscle weakness or paralysis, and in the electrocardiogram there may be flattening or inversion of the T waves. Deoxycortone is commonly given as the acetate (DCA). It is available as Deoxycortone Injection, which is an oily solution for intramuscular administration and it contains 5 mg. per ml. The dose is 2-5 mg. daily. Deoxycortone is also available as a microcrystalline suspension of

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the trimethylacetate (DCTMA, "Percorten M"). When given intramuscularly, this preparation forms a "depot", releasing approximately 1 mg. per day for each 25 mg. injected. The suspension contains 25 mg. per ml. Subcutaneous implantation of pellets of fused deoxycortone provides a "depot" from which slow release of hormone continues for 6-12 months. Each 100 mg. pellet yields about 1 mg. per day. Deoxycortone preparations are used exclusively for the treatment of primary adrenal insufficiency.

HYDROCORTISONE, the principal glucocorticoid, is made in the zona fasciculata. Corticotrophin controls its formation and release. In health 25-40 mg. are secreted per day but the output is increased by such "stresses" as exercise, mental activity, emotional upset, injury, surgical operation, and acute infection. A fall in the blood level of hydrocortisone stimulates secretion of corticotrophin which in turn increases the production of hydrocortisone by the adrenal cortex. A rise in blood level of hydrocortisone diminishes corticotrophin output.

Cortisone is closely related chemically to hydrocortisone to which it is converted in the body. It has therefore identical actions to hydrocortisone but on a weight for weight basis it is slightly less potent, 20 mg. hydrocortisone having the same effect as 25 mg. cortisone. Both these steroids undergo degradation in the liver to inert metabolites which are conjugated with glycuronic acid prior to excretion in the urine.

ACTIONS OF HYDROCORTISONE. One of the chief actions of hydrocortisone is the maintenance of the blood sugar level and the carbohydrate stores of the body. It does this by inhibiting the oxidation of glucose in the tissues (anti-insulin effect), by increasing the formation of carbohydrate from protein, and by facilitating combustion of fat and so sparing carbohydrate. In adrenal insufficiency the tendency to hypoglycaemia on fasting is corrected by the administration of hydrocortisone or cortisone. These steroids have also a weak aldosterone-like action on sodium and potassium. They are also concerned with the renal excretion of water. In adrenal insufficiency ingestion of water is not followed by a prompt water diuresis as in health unless cortisone is given. The most important effect of the glucocorticoids is the protection they

confer on the body in conditions of stress. The action is probably a fundamental one at cell level, but the details are not known. Lacking the ability to increase the output of hydrocortisone, the "stressed" adrenal-deficient patient passes into a state of profound collapse which is unresponsive to pressor agents. Intravenous injection of hydrocortisone promptly corrects these abnormalities.

*Effects of High Doses of Glucocorticoids.* When large doses of the glucocorticoids are given, there is seen the expected exaggeration of the characteristic metabolic effects. There are also other important actions. The circulating white cells are affected; eosinopenia, lymphopenia and a slight neutrophil leucocytosis occur, and there is a rapid lysis of lymphoid tissue. Secretion of gastric hydrochloric acid is stimulated and the faecal excretion of calcium is increased. A conspicuous effect is inhibition of the normal tissue changes in inflammation and repair: proliferation of fibroblasts is reduced, vascularisation impaired, normal healing delayed, inflammatory oedema reduced, and local resistance to infection diminished. Hypersensitivity reactions and immune responses are also inhibited. The increased susceptibility of adrenalectomised animals to anaphylactic shock is abolished by replacement therapy. The skin responses to an antigen such as tuberculin may be abolished or reduced by a high blood level of hydrocortisone. Bronchospasm in man is relieved by a high blood level of hydrocortisone, but the mechanism is unknown. These actions have led to the use of hydrocortisone and its analogues in a variety of non-endocrine diseases (p. 374). The prolonged administration of glucocorticoids causes atrophy of the adrenal cortex by inhibiting the secretion of corticotrophin.

PREPARATIONS OF GLUCOCORTICOIDS are available for oral and parenteral use, for topical application, and for local injection. For systemic effects cortisone is commonly given as tablets each of which contains 25 mg. Absorption from the bowel is satisfactory and the effect of one dose lasts for 4-6 hours. Injection of Cortisone for intramuscular use is a suspension of cortisone acetate 25 mg. per ml. in saline. Absorption from the

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muscles is slow and the effect lasts for 12–24 hours. Two preparations of hydrocortisone are available for systemic use: the free alcohol, 100 mg. in 20 ml. 50 per cent alcohol; and the sodium hemisuccinate, 100 mg. to be dissolved in 2 ml. water. These preparations are both given intravenously for the treatment of acute adrenal failure. The free alcohol is given as an intravenous drip, 100 mg. being added to 500 ml. 5 per cent glucose solution or saline. The hemisuccinate may be given without further dilution. Hydrocortisone Acetate Injection is a suspension containing 25 mg. in 1 ml. saline, for injection into joints and bursæ. Several preparations of hydrocortisone are available for topical use on the skin and in the eye. These vary in strength from 0.5 to 2.5 per cent and rarely give rise to systemic effects.

*Fludrocortisone* (9- $\alpha$ -fluorohydrocortisone) is a very potent variant of hydrocortisone. The glucocorticoid effect is enhanced at least tenfold, but the marked sodium retention which this compound also induces makes it unsuitable for conditions other than adrenal insufficiency.

*Prednisone* (deltacortisone) and *prednisolone* (deltahydrocortisone) cause much less sodium-retention and potassium-loss than their parent substances. In addition they are about five times more potent as glucocorticoids. Both are available as 5 mg. tablets. The dose is 5–20 mg. Several new derivatives of prednisolone, 6-methyl-prédnisolone, triamcinolone and dexamethasone have recently appeared as more potent and allegedly less toxic steroids for use as suppressives. They are still under clinical trial. Dexamethasone is about ten times more potent than prednisolone.

USES OF THE ADRENAL STEROIDS. 1. *In Endocrine Disorders.* The principal use of the adrenal steroids is as replacement therapy in adrenal insufficiency. In Addison's disease and after bilateral adrenalectomy, cortisone in doses of 12.5–50 mg. per day is given by mouth. This restores a sense of well-being and appetite improves. The weak aldosterone-like action of cortisone may be sufficient to maintain weight and blood pressure in a few patients but most require either extra salt (3–6 G. daily) or deoxycortone. The latter is commonly given as a subcutaneous implant, and its effects last for 6–12 months. The amount to be implanted is deter-

mined from the daily requirement of deoxycortone acetate (DCA) given as the oily injection intramuscularly. For each 1 mg. of DCA it is generally recommended that one 100 mg. pellet of fused deoxycortone be implanted. In practice, this method of assessment of implant dose often leads to the appearance of œdema unless the amount of salt in the diet is restricted. This may be avoided if only 80 mg. is implanted for each 1 mg. DCA required. An alternative "depot" method of therapy consists in giving an intramuscular injection of the suspension of trimethyl DCA ("Percorten M"), 25 mg. being given for each 1 mg. oily DCA required. The effect lasts for 4-6 weeks. The need for renewal of a depot of hormone is shown by a progressive fall in the patient's weight and blood pressure. Since the potent steroid fludrocortisone is endowed with both cortisone-like and aldosterone-like actions it may be used in primary adrenal insufficiency in oral doses of 0.1-0.4 mg. per day.

In hypopituitarism where deficiency of hydrocortisone occurs as a result of failure of corticotrophin secretion, cortisone 12.5 mg. is given orally twice daily; in addition thyroid and methyltestosterone may be needed.

Increased doses of cortisone are required when an adrenal-deficient patient is exposed to "stress" arising from acute infection, accident, or surgical operation. In such circumstances the increased amount of hydrocortisone required is not forthcoming from the adrenal cortex and must therefore be supplied by giving at least 25 mg. cortisone 6-hourly—in addition to other appropriate therapy. For the treatment of established acute adrenal failure or "crisis" hydrocortisone is given by intravenous drip. An ampoule containing 100 mg. of the free alcohol is added to 500 ml. normal saline. The rate of flow and the total amount to be given depend on the severity of the acute state.

In adrenal virilism due to cortical hyperplasia cortisone is an effective suppressive agent. Doses of 50-100 mg. daily are required. Prednisolone is also effective.

2. *In Non-endocrine Disease.* Apart from their use in endocrine disorders, adrenal steroids of the cortisone type are widely used empirically in many diseases where the nature of the disorder is

still obscure or cannot be influenced directly by drugs. High doses of glucocorticoids act as suppressives abolishing or diminishing in a non-specific way the tissue reactions to noxious agents. They do not influence the cause of the disease; and when steroid treatment is discontinued, symptoms and signs may recur with even greater intensity unless a remission has begun spontaneously. The high blood steroid level required to keep in abeyance the clinical manifestations of a disease carries with it special hazards, and these have to be carefully balanced against the benefits obtained by suppressive action. In this field the doses of steroids given are multiples of those used for replacement therapy in adrenal insufficiency. Initially 25-100 mg. cortisone or 5-20 mg. prednisolone are given 6-hourly and subsequently reduced to a dose sufficient to maintain the improved state.

Diseases which respond to the suppressive action of the adrenal steroids are: active rheumatoid arthritis, acute generalised lupus erythematosus, sarcoidosis and polyarteritis nodosa. Many cases of acute leukaemia in childhood yield to the action of the corticoids, but only temporarily. Acquired hæmolytic anæmia and idiopathic thrombocytopenic purpura may be controlled by steroid therapy. Ulcerative colitis, especially the first attack, is often influenced by oral corticoids, or by enemata containing the hemisuccinate of hydrocortisone. In the nephrotic syndrome diuresis may be promoted by a course of steroids. Status asthmaticus failing to yield to conventional therapy almost invariably responds to a short intensive course of steroids. Many skin conditions such as eczema, pruritus, drug eruptions, etc., are alleviated by local applications of hydrocortisone or prednisolone. Certain acute inflammatory conditions of the eye are controlled by the local use of adrenal steroids in conjunction with bacteriostatic or bactericidal agents.

*Toxic Effects of High Doses of Glucocorticoids.* The high doses of adrenal steroids required to exert a suppressive action cause a variety of toxic effects, especially when the course of treatment is prolonged. Most of the hazards can be explained on the basis of an exaggeration of the physiological effects of the steroids. Retention of sodium causes an increase of body weight, œdema, and

rise in blood pressure. Potassium loss which may produce muscle weakness, hypotension and electrocardiographic abnormalities, is especially dangerous in such conditions as ulcerative colitis where electrolyte loss (which is characteristic of this disease) may be greatly increased. Serum electrolyte levels should be checked at regular intervals and potassium supplements given if indicated. Prednisolone and prednisone are much less liable to cause electrolyte imbalance than is cortisone. Increased protein catabolism may produce striæ and a liability to bruising, and—especially in the elderly and bed-ridden—osteoporosis. Glycosuria may occur; it may be renal in type or the result of hyperglycæmia. These effects do not usually persist when therapy is discontinued. Steroids should be given with caution to patients with diabetes mellitus: they usually require additional insulin while they are on steroid therapy.

“Moon-face” appearance, mild hirsutism and acne are frequently seen during long-term administration of steroids, and there is some evidence that an increased tendency to venous thrombosis occurs.

Cortisone increases gastric acidity; occasionally acute gastric ulcers develop and these may bleed. If perforation of a peptic ulcer occurs during steroid therapy, contamination of the peritoneum may fail to excite the usually severe inflammatory reaction (peritonitis): this is called a “silent” perforation, and delay in diagnosis is almost inevitable. Such “silent” perforations also occur in ulcerative colitis. Further, it is probable that chronic peptic ulcers in a healing phase can be reactivated by cortisone. Mental changes are not uncommon, especially euphoria or mild depression. A true psychosis may also develop.

High doses of steroids reduce local resistance to infection. There is thus a risk of a latent tuberculous focus being reactivated. The circumstances resemble those mentioned above (“silent” perforation): the usual symptoms and signs of infection—such as those of pneumonia—may be suppressed, with serious or even fatal delay in diagnosis. Impaired healing of wounds and fractures does not occur unless the daily dose of cortisone is over 100 mg.

Prednisone and prednisolone seem more liable than is cortisone

to produce untoward glucocorticoid and catabolic effects. This offsets some of the advantage gained from their weak influence on electrolytes.

During a course of steroid therapy adrenal atrophy occurs from suppression of corticotrophin secretion. Abrupt cessation of treatment may lead within a day or two to acute adrenal failure ("withdrawal" syndrome) characterised by nausea, vomiting, restlessness, headache and hypotension. To prevent this the dose of steroid should be reduced gradually over a period of three or four days at the end of the course; and one or two injections of long-acting corticotrophin should be given to restore adrenal activity pending resumption of control of the adrenal by the anterior lobe of the pituitary.

### CORTICOTROPHIN

Corticotrophin (ACTH; Adrenocorticotrophic Hormone) is a naturally-occurring hormone produced by the anterior pituitary gland. It is a protein of molecular weight about 20,000 containing polypeptides which probably represent the active hormone. By special procedures two such highly active polypeptides can be isolated from ACTH—corticotrophin A and corticotrophin B (mol. wt. respectively 6,500 and 3,000).

The rate of secretion of corticotrophin is determined by the blood level of hydrocortisone. A fall in this level—such as occurs following stress—stimulates secretion of corticotrophin; a rise in the level of circulating hydrocortisone inhibits the secretion of ACTH. The injection of ACTH, or increased secretion following on stress, produces an increase in the weight of the adrenal cortex accompanied by depletion of the ascorbic acid and cholesterol normally contained in the gland. The fall in the cholesterol may be explained by the fact that it is a precursor of adrenocortical steroids. There is no evidence that ACTH acts on cells other than those of the adrenal cortex, and the hormone exerts no significant metabolic changes in the absence of its "target gland".

The *pharmacological actions* of corticotrophin are those produced by increased secretion of adrenocortical hormones (p. 372).



*Absorption, Fate and Excretion.* The activity of corticotrophin is destroyed by the proteolytic enzymes of the alimentary tract and it must be administered parenterally, either by the intravenous or intramuscular route. The hormone is rapidly absorbed from muscle and quickly disappears from the circulation following on intravenous injection, but it exerts its desired effect only on reaching the cells of the adrenal cortex. The quantitative response of the adrenal cortex to ACTH varies greatly with the route of administration and the nature of the preparation used. The available preparations of ACTH vary in biological activity and therapeutic effectiveness per unit of weight and each must be subjected to *bio-assay*; this test is based on depletion of ascorbic acid in the adrenal cortex in the hypophysectomised rat.

*Preparations and Dosage.* Corticotrophin is a sterile preparation of the hormone from the pituitary glands of domestic animals and it contains not less than 0.75 Unit per mg. It is employed as Corticotrophin Injection which is prepared by dissolving the sterile contents of a sealed container in Water for Injection containing 0.5 per cent w/v of phenol. This solution should be used within one month of its preparation and should be stored during this period at a temperature not exceeding 4° C. In therapeutic use, sustained stimulation of the adrenal cortex is necessary; this is achieved by giving 10-25 Units of corticotrophin intramuscularly every 6 hours. When the desired result is obtained the dose may be gradually reduced and the interval lengthened between injections. Alternatively corticotrophin can be administered intravenously in a daily dose of 10-20 Units, given slowly as a drip-infusion during a period of 8 hours.

It is obvious that the use of Corticotrophin Injection must cause the patient considerable inconvenience because of the need for frequent injections or even intravenous infusion. For this reason, long-acting preparations of corticotrophin have been produced. These are corticotrophin combined with protamine zinc, zinc phosphate, zinc hydroxide, or gelatin; the last is named corticotrophin gel. Their advantage consists in the slow release of the corticotrophin from the site of intramuscular injection, with the result that the long-acting preparations should be given only

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once daily. These preparations of corticotrophin should not be administered intravenously. A daily dose intramuscularly of 10–20 Units is recommended; the effect is equivalent to a total daily dose of about 100 Units of the water-soluble Corticotrophin Injection.

*Toxic Effects.* As it is a protein or polypeptide, corticotrophin may give rise to anaphylactic shock in sensitised persons. In addition it may produce the same toxic effects as those of cortisone (p. 375).

Exogenous supplies of corticotrophin depress the secretion of the endogenous hormone from the anterior pituitary gland sufficiently to cause pituitary hypoplasia; sudden withdrawal of the drug may produce symptoms of hypopituitarism and corticotrophin therapy should therefore be withdrawn gradually.

**THERAPEUTIC USES.** Corticotrophin may be used for the same conditions as cortisone (p. 374), with the exception of Addison's disease, adrenalectomy and adrenocortical hyperplasia. As a rule the convenience of the oral route of administration favours the choice of cortisone in preference to corticotrophin, but occasionally, in individual patients, the response to corticotrophin is better than that obtained from cortisone.

Corticotrophin is also used in diagnostic tests of adrenocortical insufficiency; the techniques are detailed in textbooks of endocrinology.

### PITUITARY GLAND (POSTERIOR LOBE)

Extracts of the posterior lobe of the pituitary contain at least two active fractions: (a) *oxytocin* (p. 392) and (b) *vasopressin*—which has both a pressor action and an antidiuretic effect.

**VASOPRESSIN INJECTION** is a sterile aqueous solution containing the pressor and antidiuretic principles of the posterior lobe of the pituitary body. It contains 20 Units of pressor activity per ml. From the medical practitioner's point of view the antidiuretic effect of this preparation is much more important than the pressor action. The antidiuretic principle regulates renal

tubular reabsorption of water (p. 50). The normal kidney is extremely sensitive to the effect of antidiuretic hormone: a fall in the output of urine follows the administration of as little as 0.005 Unit in man. A few minutes after giving an injection of vasopressin, vasoconstriction is apparent in the superficial capillaries and arterioles and there is a rise in blood pressure. However, the dose of vasopressin which is required to produce vasoconstriction in man is very much greater than that required to produce the antidiuretic effect. Hence, in spite of its name, Vasopressin Injection is not the drug of choice if the object is to raise blood pressure in patients suffering from arterial hypotension; the sympathomimetic amines (p. 134) are more effective and act more selectively. Again, following the Injection of Pituitary (Posterior Lobe) or Vasopressin Injection certain side-effects are apt to occur and these may occasion some distress: the face becomes blanched; and increased peristalsis often causes nausea, abdominal cramp and evacuation of the bowel. The most serious side-effect is constriction of the coronary arteries and in patients with established coronary artery disease there may be anginal pain. These patients should not receive vasopressin except for the treatment of diabetes insipidus—and here only small doses are needed.

*Absorption, Fate and Excretion.* If it is given by mouth the antidiuretic principle is digested and destroyed by trypsin: it must therefore be administered by some other route. The usual method is to give Vasopressin Injection subcutaneously or intramuscularly, but it may also be administered intranasally as snuff of Powdered Pituitary (Posterior Lobe). Soon after absorption, the antidiuretic principle is rapidly inactivated probably in the liver and kidney.

**THERAPEUTIC USES AND DOSAGE.** The principal use of Vasopressin Injection is in the treatment of diabetes insipidus. In this disease there is a reduced secretion of endogenous antidiuretic hormone. In consequence the output of urine increases—often tenfold. The patient lives in constant danger of serious dehydration characterised by thirst: he therefore drinks large volumes of water and inevitably suffers the inconvenience of polyuria day

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and night. All these symptoms can be abolished by ensuring that the patient receives an adequate supply of antidiuretic hormone. The official dose is 0.25–0.75 ml., equivalent to 5–15 Units. Injections of an aqueous solution give only temporary benefit owing to the rapid absorption and inactivation of the antidiuretic principle. Intramuscular injection of vasopressin tannate in oil ("Pitressin Tannate")—daily or on alternate days—obviates this disadvantage, as the active principle is released slowly. The dose of this preparation varies with the needs of the individual patient, but it usually ranges from 1.5–5 Units daily.

Vasopressin Injection may also be used in order to promote peristalsis and abolish the state of *ileus*. Treatment on these lines is justified if the essential abnormality is flaccidity of the bowel wall resulting from lack of pressor substances. The use of vasopressin—or other drugs which cause vigorous peristalsis—is contra-indicated if the ileus is the consequence of intestinal obstruction associated with organic disease. The dose employed is 5–10 Units of this water-soluble preparation.

## FEMALE SEX HORMONES

Female sex hormones belong to two main groups, the oestrogens and the progestogens. Oestrogens can reproduce the phenomenon of oestrus in ovariectomised animals (for example in rodents); they are responsible for the secondary sexual characteristics in woman, for the physiological changes that occur in the endometrium—especially in the first half of the menstrual cycle; and after the first week of pregnancy they are present in the blood in rising concentration. The progestogens play a part in the initiation and maintenance of physiological changes in the uterus and breasts in pregnancy, and govern the endometrial changes that occur in the second half of the menstrual cycle.

Natural oestrogens and progestogens are produced in the ovaries: oestrogens are derived from the Graafian follicles, the ovarian stroma and corpora lutea; and progestogens from the corpora lutea and probably from the placenta. Both oestrogens and progestogens are produced in small quantities by the adrenal cortex, and in the male by the testis.

## THE ŒSTROGENS

**ACTIONS.** At puberty in the female increasing œstrogen output from the ovaries is responsible for the appearance of the secondary sexual characteristics—breast development, skin maturation, changes in body contour, and the appearance of pubic and axillary hair. At the same time epiphyseal closure is initiated, the myometrium and endometrium proliferate, the Fallopian tubes develop and the vaginal epithelium becomes keratinised. Œstrogens also play a fundamental role in menstruation and pregnancy.

The pharmacological actions of the œstrogens can be predicted from the physiological actions just described. Administration of œstrogen causes proliferation of the myometrium and of the endometrium. A rapid reduction of œstrogen dosage causes endometrial shedding (withdrawal bleeding). In the immature female sexual maturation occurs. Osteoblastic activity is stimulated and epiphyseal closure is accelerated. The output of gonadotrophin from the anterior pituitary is reduced, but ACTH output may be increased. Œstrogens have a slight tendency to produce sodium and water retention by an action on the renal tubule, and have a mildly anabolic action on protein metabolism. They also tend to antagonise the virilising action of the androgens.

The role of the œstrogens in carcinogenesis is complex and obscure. Some breast and uterine cancers seem to be “œstrogen dependent”: when deprived of œstrogen (surgical removal of ovaries and adrenals) the growth of these tumours may be retarded or temporarily arrested. Occasionally the growth of breast cancers occurring in women after the menopause appears to be inhibited by the therapeutic administration of œstrogens. In the male administration of œstrogens often causes recession of primary and secondary prostatic carcinoma—probably by inhibition of gonadotrophin output which in turn leads to a fall in androgen secretion, though there may also be a peripheral action.

**PREPARATIONS.** Three groups of preparations are available: (1) natural œstrogens; (2) semi-synthetic œstrogens; and (3) synthetic œstrogens.

Œstrogens in all three groups are largely degraded in the liver and excreted conjugated in the urine.

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*Natural Œstrogens.* The three main natural œstrogens are œstrone, œstriol and œstradiol. They are steroids with a basic structure similar to that of the adrenocortical and the androgenic hormones. The actual ovarian hormone is probably œstradiol; œstrone and œstriol being excretion products which nevertheless retain their biological activity. The natural œstrogens are very expensive to prepare; also they lose at least 80 per cent of their potency when given by mouth. Their solubility in water is low and therefore they are usually given by intramuscular injection as a solution in oil. The natural œstrogens are free alcohols and form esters with propionic, benzoic, palmitic and other organic acids. The unmodified hormones are quickly absorbed and quickly excreted after injection, and exert a transient effect; but the esters, of which œstradiol monobenzoate and œstradiol dipropionate are the most commonly used, exert a more sustained action lasting for several days. These esters are also available as fused pellets for subcutaneous implantation. A mixture of water-soluble conjugated œstrogens has been prepared from the urine of pregnant mares. It includes equilin sulphate, sodium œstrone sulphate and related œstrogens. It is available as "Premarin" in tablets of 0.625 mg. and 1.25 mg. It has half the potency of stilbœstrol but side-effects are less troublesome; it is relatively expensive. Pharmaceutical preparations (BP and BPC) of the natural œstrogens are listed elsewhere (p. 720).

*Semi-synthetic Œstrogens.* The only important semi-synthetic œstrogen is Ethinylœstradiol, which is highly effective when taken by mouth. It is twenty times more potent than stilbœstrol. The tablets are official (0.02 mg.): the dose is 0.01–0.1 mg. daily.

*Synthetic Œstrogens.* Stilbœstrol, the first synthetic non-steroid œstrogen, is highly effective when given by mouth. It is an inexpensive preparation. Other synthetic œstrogens include *stilbœstrol dipropionate*, which has a prolonged action lasting several days when given by injection, *dienœstrol* which is used in doses approximately four times that of stilbœstrol, and *hexœstrol*. The side-effects of these preparations are important. Stilbœstrol,

and to a lesser effect the other synthetic œstrogens, produce nausea (occasionally vomiting) in about one-fifth of patients, especially postmenopausal women; diarrhœa also occurs, but it is exceptional. Such side-effects are rare in men and in pregnant women. Hexœstrol, which has a very weak action compared with that of stilbœstrol, rarely causes nausea or vomiting.

*Chlorotrianisene* is a non-steroid synthetic œstrogen. When given by mouth it is stored in the body fat in an inactive "pre-œstrogen" form. It is slowly released and converted in the liver to an active substance with œstrogen-like activity. After a course of treatment the depot effect may last several months.

There are official Stilbœstrol Tablets (0.5 mg.). The dose varies from 0.5 mg. to 1 mg. daily for menopausal symptoms, to 10-15 mg. daily to inhibit lactation or for carcinoma of the prostate. It can also be given parenterally as Stilbœstrol Dipropionate Injection (5-10 mg. intramuscularly). The doses of the other preparations mentioned above are as follows: Dienœstrol 0.5-10 mg. daily (as tablets of 1 mg.); Hexœstrol 1-5 mg. daily (as tablets of 1 mg.); and Chlorotrianisene 12-48 mg. daily (as a solution in oil, dispensed in capsules each containing 12 mg.).

**CHOICE OF PREPARATION.** The synthetic œstrogens are inexpensive and very effective when given by mouth, and should normally be the type of œstrogen used. If nausea and vomiting are troublesome, ethinylœstradiol may be tried, or especially for long-term therapy in the menopausal patient, chlorotrianisene. The synthetic œstrogens are somewhat less effective by injection than are the natural hormones, but when parenteral therapy is indicated, appropriate adjustments can be made in dosage. Moreover, the natural œstrogens are much more expensive.

#### CLINICAL USES OF ŒSTROGENS

The most frequent use of œstrogens is in the management of the menopausal syndrome: both psychic upset and unpleasant somatic disturbances are relieved—partly by a direct effect and perhaps partly by a reduction in FSH output. They may be used to inhibit lactation. Short courses are of value in kraurosis vulvæ

## PHARMACOLOGY OF THE ENDOCRINE GLANDS

and senile vaginitis; for this purpose stilbæstrol pessaries may also be used.

Replacement therapy with œstrogens may be necessary in primary amenorrhœa accompanied by genital hypoplasia and sexual underdevelopment. Œstrogens may also be used in the management of postmenopausal osteoporosis in the female, and in certain types of breast cancer.

### THE PROGESTOGENS

Progesterone is a naturally-occurring steroid hormone which is secreted by the corpus luteum during the second half of the menstrual cycle and is responsible for transforming the endometrium, previously sensitised by œstrogen, to the secretory pre-gravid phase necessary for the reception of the fertilised ovum. It has also a role in the maintenance of pregnancy and in the development of breast alveoli during pregnancy. In the second half of pregnancy it is probably secreted by the placenta.

Progesterone is converted in the body into pregnanediol. This is conjugated and is excreted by the kidney; it can be measured chemically in the urine.

Progesterone is inactive by mouth. It is therefore given as an oily solution by intramuscular injection, or by implant. Ethisterone, a synthetic steroid, is active by sublingual administration in doses about six times greater than the parenteral dose of progesterone. It is also very weakly œstrogenic and androgenic. In the official Injection, 10 mg. of progesterone is contained in 1 ml. of oil: the dose is 5–20 mg. daily, by intramuscular injection. Ethisterone is available as tablets containing 25 mg. The dose is 25–100 mg. daily.

*Uses of Progestogens.* Progestogens are used, but without conspicuous success, in the treatment of habitual abortion and in some forms of dysmenorrhœa and amenorrhœa.

### ANDROGENS

The androgens are the hormones responsible in the male for the development of the sexual organs and the secondary sex characteristics. The most important androgen is testosterone;



this hormone is secreted by the testes, the amount being controlled by the gonadotrophic hormone of the anterior pituitary gland. Androsterone and dehydroandrosterone are metabolic degradation products of testosterone: they have considerably less androgenic activity than testosterone and they are excreted in the urine. Androgenic compounds and their precursors have been isolated from the ovary and the adrenal as well as from the testis.

**PHARMACOLOGICAL ACTIONS.** The most important actions of the androgens are on the sex organs and secondary sex characteristics. In hypogonadal or prepubertal males repeated administration of androgen eventually produces growth of the secondary sex organs as well as development of the secondary male sex characteristics. In hypophysectomised rats spermatogenesis can be maintained by the administration of androgens, but there is no evidence that a similar result occurs in man. When testosterone is skilfully used as a form of substitution therapy the results are often excellent. Sustained overdosage, however, leads to automatic readjustment in endocrine activity: there is a strong tendency for *endogenous* supplies of the hormone to diminish when relatively large quantities are being introduced into the body for therapeutic effects. Further, after a period of prolonged inactivity the tissues which normally secrete the hormone may undergo atrophic change. It follows that exogenous supplies of hormone must be accurately adjusted to the requirements of the individual patient: the aim is to give enough hormone to compensate for the deficiency and to avoid the irreversible consequences of prolonged overdosage. Testosterone given to a normal male may cause disappearance of the testicular interstitial cells and may arrest spermatogenesis. High doses of testosterone can greatly diminish the output of gonadotrophins from the anterior pituitary.

In the female androgens produce masculinisation, indicated by growth of the clitoris, hirsutism, deepening of the voice, increase in muscle bulk, and an acneform eruption. By depressing the output of pituitary gonadotrophins, androgens can suppress ovulation and prevent the development of a proliferative endometrium. Androgens also produce a progestational effect on the uterine mucosa by a direct action.

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Protein anabolism is stimulated by androgens, especially in hypogonadal subjects. There are reports of increase in weight in debilitated elderly patients following the administration of androgens. Balance studies have shown that the loss of nitrogen, potassium and phosphorus in the urine is reduced by the action of androgens. New steroid compounds have been designed in an attempt to exploit this action on metabolism. The objective is to discover compounds which promote maximal protein anabolism though possessing minimal androgenic activity. Examples of such compounds are mentioned later in this chapter.

Androgens, like the  $\alpha$ strogens, promote the reabsorption of extracellular electrolyte by the renal tubules, but the production of  $\alpha$ edema does not usually complicate their therapeutic use in practice. The effects of androgens on the skeleton vary with the dose employed. They promote growth of bones and have been employed in the treatment of senile osteoporosis; in the growing child high doses accelerate closure of the epiphyses and thus the inappropriate use of androgens in the treatment of "dwarfism" may retard growth by promoting premature fusion of the epiphyses.

*Toxic Effects.* In women, large doses produce masculinisation and in adolescents of either sex premature closure of epiphyses may also occur. In adult fertile males spermatogenesis may be suppressed, although the changes are reversible.  $\alpha$ edema may develop during prolonged treatment with large doses of androgens. Patients receiving methyltestosterone occasionally develop jaundice which is the result of intracanalicular biliary stasis. Androgens should not be used in the presence of carcinoma of the prostate.

*Absorption, Fate and Excretion.* Testosterone and methyltestosterone are readily absorbed from the gastro-intestinal tract, but they are largely metabolised in the liver to less active steroids (androsterone and *iso*androsterone) or to the inactive etiocholanolone which are excreted in the urine in conjugated form. Methyltestosterone can be given sublingually. Testosterone propionate in oil injected intramuscularly is effective for 24-28 hours but

when an aqueous suspension of a crystalline preparation of testosterone is given intramuscularly, absorption is slow and the therapeutic effect is maintained for about 7 days. The most satisfactory method of obtaining a sustained action—lasting about 6 months—is by the subcutaneous implantation of pellets of testosterone.

*Bio-assay and Unitage.* The most commonly employed method of bio-assay is that of promoting comb growth in capons. The *International Unit* of androgen activity by this test is that of 100 micrograms of crystalline androsterone.

*Preparations and Doses.* *Testosterone* is a white crystalline powder which has the actions and uses of the androgens. It is synthesised for therapeutic use. It is  $17\beta$ -hydroxyandrost-4-en-3-one and may be prepared from dehydroepiandrosterone, a substance obtainable from sterols such as cholesterol. The best method of administration is in the form of subcutaneous Testosterone Implants, each being a sterile cylinder of 100 mg. of testosterone without the addition of any other substance. A dose of 600 mg. given in this manner is effective for about 6 months.

*Testosterone Propionate*, a white crystalline powder (produced synthetically), is given by intramuscular injection of an oily solution. The official dose is 5–25 mg., and in the treatment of hypogonadism 10–50 mg. is given daily until symptoms of deficiency subside and thereafter a smaller maintenance dose or a subcutaneous implant of testosterone may be given. “Perandren M Crystules” is a preparation for intramuscular injection of microcrystalline testosterone *isobutyrate* in an aqueous solution.

*Methyltestosterone* is the orally effective form of testosterone and may be used for maintenance therapy in hypogonadism, especially when the androgenic requirement is small. The dose is 25–50 mg., and it is available as a Tablet of Methyltestosterone containing 5 mg. methylandrostanolone. Methandriol and norethandrolone are stated to have low androgenic activity while promoting protein anabolism. These and related drugs are given

## PHARMACOLOGY OF THE ENDOCRINE GLANDS

orally and have been used in the treatment of debilitated patients who are underweight; the status of these preparations as therapeutic agents has not yet been fully determined.

**THERAPEUTIC USES OF THE ANDROGENS.** The androgens are used mainly as replacement therapy in castrated males and in primary hypogonadism or secondary testicular failure. In primary hypogonadism in boyhood, therapy should not be started until the time when puberty would normally occur. They are of no value in the treatment of undescended testes: here rational therapy would consist in the administration of gonadotrophin, but a satisfactory preparation of this hormone is not yet available.

In the treatment of dwarfism resulting from insufficiency of the anterior pituitary gland, administration of androgens undoubtedly stimulates growth. Reference has already been made, however, to the danger of premature epiphyseal fusion; and androgen therapy must be carefully controlled by frequent radiographs of the long bones. Senile osteoporosis has been treated by androgens; in women, the dose must be kept below that which produces masculinisation. In patients with mammary carcinoma in whom it has been decided that radiotherapy and surgery are of no value, androgens may be given. They are administered in large doses and testosterone propionate may be given intramuscularly thrice weekly in doses of 50–100 mg. If osteolytic metastases are present, this therapy may produce hypercalcaemia with subsequent deposition of calcium in the urinary tract; hypercalcaemia is an indication to withdraw the hormone.

## PARATHYROID

Parathyroid is no longer included in the BP. Its omission does not imply that pharmaceutical preparations of parathyroid are inert. There is no doubt about the potency of such products when properly prepared and administered parenterally. There are, however, serious limitations to the therapeutic usefulness of parathyroid hormone. It is noteworthy that although this substance has been deleted from the BP, it is still official in the USP and is retained in the BPC.

A pharmaceutical preparation of parathyroid hormone is an

aqueous solution containing the water-soluble principles of the parathyroid glands. When injected parenterally, parathyroid hormone increases the calcium content of the blood serum. Preparations for therapeutic use are biologically standardised. Thus 100 parathyroid units (USP) raise the calcium content of 100 ml. of the blood serum of normal dogs by 1 mg. during the period extending from the 16th to the 18th hour after administration.

*Actions and Uses of Parathyroid Hormone.* Details regarding the effects of parathyroid hormone are set out in standard textbooks of physiology and biochemistry. Briefly, the main action of this hormone is to control calcium metabolism and phosphorus metabolism. When an animal is deprived of its parathyroids (by surgical operation) there is retention of inorganic phosphate by the kidney and a reciprocal fall in serum calcium concentration. This leads to the state of hypocalcæmic tetany. The parenteral administration of parathyroid hormone abolishes the clinical manifestations of tetany, and simultaneously the blood biochemistry slowly returns to normal. This substitution therapy constitutes the sole indication for the use of parathyroid hormone in man. Disorders of calcium and phosphorus metabolism unrelated to parathyroid dysfunction do not respond to therapy with this preparation.

Even when parathyroid hormone is specifically indicated, it has certain shortcomings as a therapeutic agent. First, it produces its effects *slowly*, and therefore (having regard to the patient's need for immediate relief) its use is best supplemented by giving a suitable preparation of calcium intravenously. Secondly, repeated administration of parathyroid hormone leads to the development of *tolerance* and a rapid falling-off in the effectiveness of treatment. Hence, although there may be justification for administering parathyroid hormone at the outset of treatment to a particular patient suffering from tetany, once the acute symptoms have been brought under control (usually by means of calcium gluconate intravenously) there is rarely any justification for giving additional injections of the hormone. Long-term therapy consists in giving a diet rich in available calcium and poor in phosphorus, supplemented by calciferol or by dihydrotachysterol.

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*Preparations and Dosage.* The dose of Parathyroid Injection (USP) is 100–300 Units intravenously. Although maintenance doses of 20–40 Units intramuscularly daily are also mentioned, this form of therapy is not recommended; the reasons are stated above.

The use of large doses of parathyroid hormone intravenously calls for careful biochemical control: the serum calcium should not be allowed to rise above 12 mg. per cent if the toxic effects associated with hypercalcaemia are to be avoided.

## CHAPTER 13

### DRUGS ACTING ON THE UTERUS

**INTRODUCTION.** The uterus exhibits spontaneous rhythmic movements in the pre- and postpubertal years of life. Activity varies in relation to the phase of the menstrual cycle. There is greatly increased movement during pregnancy; and contractions of uterine muscle are, of course, of special importance during parturition. The pattern of motor activity in the uterus varies greatly among different species of animals; and within the same species there are wide variations between individuals. As far as laboratory animals are concerned, such variations are noteworthy because they indicate the limited significance of the results of experimental work carried out on the effects of drugs on the uterus in lower animals. Although the uterus is innervated from both the sympathetic and the parasympathetic divisions of the autonomic nervous system, severance of all these vegetative nerve fibres does not change the rhythmic movements of the uterus to any important extent. Further, although the effects of sympathomimetic and parasympathomimetic drugs on the uterus are readily demonstrable, they are not conspicuous pharmacologically and they are of little importance to the medical practitioner. Drugs which have powerful stimulating effects on the uterus act directly on the muscle itself: the most important are Oxytocin Injection (from an extract of the posterior pituitary gland) and the alkaloids of ergot.

OXYTOCIN is one of the hormones obtained from the posterior lobe of the pituitary (see Hormones, Chapter 12). It is a peptide and it can be separated from the parent protein which is secreted in the neurohypophysis. Oxytocin can be used as the Oxytocin Injection. Alternatively the Injection of Pituitary (Posterior Lobe) may be given for its oxytocin content, but in this case the effects of the other hormones (vasopressor and antidiuretic) are also produced. Oxytocin has a direct stimulating action on uterine muscle,

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increasing the force of contraction. The intensity of this action is determined by a variety of circumstances. The sensitiveness of the uterus to stimulation by oxytocin is affected by the presence of sex hormones—the œstrogens and progesterone. This is a matter of great importance and interest to the physiologist, and to some extent it must be borne in mind by the practitioner—though he employs oxytocin in a restricted field of therapeutics. In the human subject the response of the non-pregnant uterus is greatest during the first two weeks of the menstrual cycle. More important is the fact that the sensitiveness of the uterus to oxytocin is increased progressively during pregnancy and reaches a maximum at full term and immediately postpartum. The non-pregnant human uterus responds more readily to stimulation by vasopressin (p. 379) than to oxytocin. In pregnancy, however, as already stated, the susceptibility of the human uterus to oxytocin becomes more apparent, and as full term approaches this effect is much greater than the response to vasopressin. The only point of possible practical importance in this is that if Injection of Pituitary (Posterior Lobe) were used in the late stages of pregnancy, the response of the human uterus would be principally attributable to the effect of oxytocin, but also partly due to the action of vasopressin.

Oxytocin has an important action in relation to the mammary gland. The myoepithelium, which on contraction expresses milk from the mammary alveoli and ducts, is stimulated by oxytocin; the response is known as milk “letdown”.

In pregnant women there may be a reduction in arterial systolic blood pressure amounting to 50 mm. of mercury following the intravenous injection of 3 Units of oxytocin.

*Absorption, Fate and Excretion.* Oxytocin must be administered parenterally as it is rapidly destroyed by enzymes in the alimentary tract. The metabolic fate in the body is unknown, but the intensity of action can be readily controlled when the drug is given by slow intravenous infusion.

The official preparation is Oxytocin Injection (“Pitocin”), the solution containing 10 Units of oxytocic activity in 1 ml. For the control of postpartum hæmorrhage 2–5 Units are given by sub-



cutaneous or intramuscular injection; for the induction of labour, or to stimulate uterine contractions during labour, 1-5 Units are given by intravenous infusion in 500-600 ml. of Dextrose Injection.

**THERAPEUTIC USES.** In general the practical applications of these pharmacological (or physiological) phenomena can be anticipated, but the precise indications for intervention can be defined only by consideration of the needs of the individual patient and all the circumstances of her case. Thus it is possible to precipitate the onset of labour ("induction of labour") by giving oxytocin towards full term and this is *occasionally* justified when, in the judgment of the obstetrician, the uterine muscle is not showing sufficient spontaneous activity (onset of uterine inertia). On the other hand, the circumstances may warrant a more conservative approach consisting essentially in taking steps to ensure a few hours sleep so that spontaneous activity of the uterus may be allowed to return. In any case oxytocin must not be given until the os uteri is fully dilated, lest contractions of the uterine muscle—greatly increased under the influence of oxytocin—should cause injury to the foetus, delayed parturition and even rupture of the uterus.

The main indication for oxytocin is in the prevention and the control of postpartum hæmorrhage in the third stage of labour after the birth of the child and extrusion of the placenta. In practice, however, oxytocin is now less frequently used: ergometrine (p. 396) is preferred—injected parenterally in anticipation of the need and as determined by the obstetrician.

**ERGOT** is the sclerotium of the fungus *Claviceps purpurea* which sometimes infects the rye plant. The hyphal filaments of the germinating spores penetrate into the ovary of young rye, and eventually the typical black-purple body of the sclerotium is produced. In commerce, ergot is imported principally from Spain and Portugal, but it is also available in Central Europe.

This drug is of great historic interest. Before the toxic actions of ergot were appreciated, infected grain was widely consumed in rye flour and resulted in the disease called "ergotism". The

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origin of this malady remained a mystery and for many centuries in mediæval times it was enshrouded in superstition. The alkaloids of ergot produce vasoconstriction, and the sustained ischæmia of the tissues of the extremities had two remarkable effects: inadequate nutrition of the peripheral nerves caused paræsthesiæ and a burning sensation in the hands and feet; the reduced blood supply to the tissues also resulted in chronic dry gangrene with spontaneous separation of the blackened and shrivelled digits or larger members. The layman's name for this malady was "St. Anthony's Fire". It was so-called because a visit to the shrine of the saint often brought relief. The therapeutic effect was of course derived from the pilgrimage—which necessitated the patient's removing himself to a different part of the country where the bread was made from uninfected flour. Another important toxic effect was a high incidence of abortion and stillbirth which were the results of the stimulating effect of ergot on the muscle of the gravid uterus.

*Active Principles.* Ergot contains a large number of active substances that are of great interest to pharmacologists and biochemists. There are six isomeric pairs of alkaloids. The most important of these are *ergometrine* (syn. ergonovine) and *ergotamine*; ergotoxine was originally thought to be a pure chemical substance, but it has been shown to be a mixture of alkaloids (principally ergocornine). Among the other chemical substances which have received much attention from experimental workers are numerous amines including histamine and tyramine; and choline and acetylcholine are also present.

**PHARMACOLOGICAL ACTIONS.** The alkaloids of ergot are grouped as follows: (*a*) the amino-alkaloids: these are compounds of high molecular weight which, on hydrolysis, yield an amino acid among other products (for example ergotamine); (*b*) the amine alkaloids which consist of lysergic acid linked with a single amine (for example, ergometrine). From the clinical viewpoint there are no important actions of ergot other than those on the uterus and the blood vessels, and these effects are adequately illustrated by the pharmacological actions of ergometrine and ergo-

tamine respectively. It is in fact remarkable that the powerful action of ergot alkaloids on the smooth muscle of the uterus and of the blood vessels does not occur in other viscera to any significant extent.

*Action and Uses of Ergometrine on the Uterus.* Ergometrine increases the activity of uterine contractions. The effect is particularly obvious in the gravid uterus. Small doses cause a simple increase in the force of contraction; subsequent relaxation occurs normally. Large doses cause powerful contractions, and in excessive amounts the alkaloid produces tetanic spasm of the uterine muscle. This action is most likely to occur in the gravid uterus and especially when parturition is proceeding or is imminent. It is this tendency to produce tetanic spasm of the wall of the uterus which constitutes a danger to the fœtus: the force of contraction impedes placental circulation and may cause death of the fœtus by asphyxia. Hæmorrhage occurring after the birth of the infant (postpartum hæmorrhage) is often attributable to lack of tone in the uterine muscle. The prompt administration of ergometrine intravenously produces sudden tonic contraction of the uterus and closure of the venous sinuses which are the site of the bleeding: this is an extremely effective therapeutic procedure and may indeed be life-saving.

*Preparations and Dosage.* Ergometrine Maleate may be given orally (as a solution) in a dose of 0.5–1 mg. Uterine stimulation occurs about 8 minutes after a therapeutic dose. Injection of Ergometrine Maleate is administered by intramuscular injection of 0.25–1 mg. and this acts in about 4 minutes; given intravenously as 0.125–0.5 mg. vigorous contraction of the uterus follows within one minute.

*Action and Uses of Ergotamine on Blood Vessels.* Ergotamine is a powerful vasoconstrictor, whereas this action is relatively weak in the case of ergometrine. It acts directly on the muscle of the vessel walls. This action can be demonstrated in the living animal and also on perfused vessels. One result of such vasoconstriction—if it is prolonged—is to cause serious ischæmia of tissues and

## DRUGS ACTING ON THE UTERUS

there is thus a risk of gangrene of the extremities—especially in man. The effects of vascular occlusion may be aggravated by the toxic changes which ergotamine often produces on capillary endothelium: this increases the intravascular obstruction and still further hinders blood flow.

An important therapeutic application of this pharmacological action is in the treatment of migraine. In this disability the severe headache appears to be associated with excessive pulsation in the cranial arteries. The vasoconstrictor effect of ergotamine has therefore been applied therapeutically to reduce the amplitude of the beat. The relief obtained by prompt parenteral injection of ergotamine is often very striking. The value of ergotamine in migraine is enhanced by giving caffeine—which also has a vasoconstrictor effect on the cranial arteries.

*Preparations and Dosage.* Ergotamine Tartrate should be given at the onset of an attack of migraine. The dose of the Injection is 0.25–0.5 mg. subcutaneously or intramuscularly. The Tablet of Ergotamine Tartrate contains 1 mg., and 1 or 2 tablets may be given sublingually.

## CHAPTER 14

### DRUGS ACTING ON THE ALIMENTARY SYSTEM

#### BITTERS.

BITTER-TASTING substances acting on taste buds in the tongue can reflexly cause an increased secretion of saliva and gastric juice. The response to this stimulation is reported to be greater in the cachectic than in the normal animal. This increase in flow of saliva and gastric juice may improve appetite and digestion. These substances have no effect when given by a stomach tube, but they are active when used as a mouth-wash, so it is obvious that the sensory side of the reflex arc is in the mouth. They are used about half an hour before meals to increase appetite and to enhance digestive functions.

The "simple bitters"—*Calumba* and *Quassia*—are those which contain only bitter principles and no aromatic substances; they have no smell. Both of these can be prescribed with iron salts as they contain no tannic acid. In general, however, it may be said that the compounding of medicines in this way is to be discouraged: the management of the case is simplified by giving the bitter tonic before meals and the iron after meals. The "aromatic bitters" include extracts of orange peel, lemon peel and gentian root; they combine an aromatic flavour with a bitter taste. Compound Tincture of Gentian (2–4 ml.) is the preparation commonly used. It is slightly aromatic and its bitter taste is not sufficiently intense to be disagreeable.

Other bitter-tasting substances like strychnine and quinine are also used in small doses (a mere trace) to produce this effect. Unsweetened or "dry" sherry (as distinct from the dark sweet sherry) is a popular appetiser taken before meals. Another palatable aperitif is gin with "bitters" or a "tonic" water—which contains quinine. It is probable that few people who are in the habit of taking these slightly bitter beverages would continue to do so if the aperitif contained no alcohol.

## DIGESTIVES

There is little that drugs can do to facilitate digestion or absorption, but some help can be given where the necessary enzymes are deficient.

**PEPSIN.** The important juices secreted into the stomach are hydrochloric acid and pepsin. In an acid medium pepsin digests protein. Animal pepsin for therapeutic use is prepared from the fresh gastric mucosa of the pig, sheep or calf: it is a light yellowish-brown powder. Pepsin may be given in doses of about 0.5 G. In order to enhance the action of the enzyme dilute hydrochloric acid is given (4 ml. diluted in about 200 ml. of diluted orange juice). Pepsin is now seldom used in the treatment of gastric disorders: dyspeptics rarely lack pepsin, and achylia gastrica per se causes no symptoms.

**HYDROCHLORIC ACID** converts pepsinogen to pepsin and also supplies the acid medium essential for the proteolytic action of pepsin. The high acidity of the gastric juice ( $pH$  3-4) accounts for the fact that stomach contents are normally sterile. The functioning of the pyloric sphincter appears to be affected by the varying concentrations of hydrochloric acid in the stomach, but this is only one factor - and probably not the most important. The presence of acid in the duodenum is reported to stimulate gastric secretion and increase the secretory activity of the pancreas and liver. Iron and calcium are more completely absorbed if the upper portion of the intestinal tract has an acid reaction. It is noteworthy, however, that about 10 per cent of the adult population have no free hydrochloric acid in their stomach secretion and yet appear to be at no disadvantage on this account. Achlorhydria accompanies many organic diseases such as gastric carcinoma and pernicious anæmia. In the latter disease no hydrochloric acid is secreted even after the injection of histamine (histamine-fast achlorhydria). No benefit appears to be derived from the use of Dilute Hydrochloric Acid for patients suffering from gastric carcinoma or pernicious anæmia and it is rarely prescribed for such patients. Dilute Hydrochloric Acid is used in the treatment of "gastrogenous

diarrhœa". This is a rare condition in which achlorhydia appears to be the abnormality accounting for early morning diarrhœa. The diagnosis is made by exclusion of the common causes of diarrhœa and by showing that the symptoms are abolished by giving adequate doses of hydrochloric acid.

**BILE.** Bile preparations used therapeutically are not natural bile salts but partially synthetic derivatives of the bile acids. Dehydrocholic acid is the most important. Bile salts aid in the emulsification and absorption of fats and increase the activity of pancreatic lipase. They are also necessary for the adequate absorption of Vitamins A, D, E and K (the fat-soluble vitamins) and of carotene. Bile salts diminish intestinal putrefaction and accelerate peristalsis. The most important pharmacological action of bile preparations such as dehydrocholic acid is that of stimulating the natural flow of bile (choloretic action). The bile salts do not increase the excretion of bile pigments already released from the liver: the administration of bile salts is therefore useless as a means of accelerating the clearing of obstructive jaundice.

The intestine is sometimes deprived of bile because the secretion is diverted to the body surface or elsewhere by fistulæ or by surgical drainage. In these circumstances the oral administration of bile salts is logical replacement therapy, diminishing the risk of malabsorption of fat and a resulting deterioration in the patient's physique. Further, after absorption the bile salts increase bile flow and promote better drainage from the biliary tract. In obstructive jaundice where fat-soluble vitamin deficiency is suspected a dose of 2 G. of bile salts given with the vitamins aids their absorption. Bile salts (0.4 G.) may be given three times daily in an attempt to prevent recurrence of symptoms in cholelithiasis. A suitable preparation is Sodium Tauroglycocholate BPC, and it is dispensed in gelatin capsules. Dehydrocholic acid has been used in diseases of the biliary tract to induce a copious flow of bile and thus prevent infection of the biliary passages, for example in cholecystitis and non-calculous cholangitis. It is difficult, however, to assess the therapeutic value of such procedures.

Sodium dehydrocholate given rapidly intravenously in a dose of 3-5 ml. of a 20 per cent solution has been employed to measure

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circulation time: it causes a bitter taste in the mouth, and this is taken as the "end point".

**PANCREATIN.** This is an alcoholic extract of animal pancreas and it contains the enzymes trypsin, amylase and lipase. Trypsin breaks down protein into polypeptides and amino acids; amylase converts starch into maltose and lipase splits fats into fatty acids and glycerol. Pancreatin acts only in an alkaline medium, is destroyed by acid and should be given in keratin-coated capsules in a dose of about 0.5 G. It appears to be of some value as replacement therapy where naturally occurring pancreatic secretion is inadequate, for example in chronic pancreatitis and in patients with obstruction of the pancreatic duct.

## EMETICS

An emetic is a drug which is deliberately used to produce vomiting. The act of vomiting is under the control of a special centre in the medulla. Under abnormal conditions many viscera emit stimuli which excite the vomiting centre, the impulses passing first through a chemoreceptor trigger centre on the surface of the medulla. Irritation of the gastric mucosa by means of a drug such as ipecacuanha is an example of this kind of pharmacological action. On the other hand apomorphine hydrochloride acts directly on the chemoreceptor trigger zone. Although the physiology of nausea and vomiting is of great importance to the clinician, emetics have a very restricted use in therapeutics, and they warrant only brief comment.

**APOMORPHINE** is an alkaloid which is remarkable for its specific stimulating action on the chemoreceptor trigger zone: it is thus classed as a central emetic. It is given by subcutaneous injection (10 mg.) and within a minute nausea and vomiting develop suddenly. In smaller doses (1 mg.) apomorphine by its action on the vomiting centre induces through the secretory fibres of the vagus an increase in the mucous secretion of the bronchial glands. Apomorphine given in these mildly nauseating doses may be said to be an expectorant, but it is hardly ever used in this way because patients will not tolerate recurring bouts of nausea.



A strong solution of common salt (a dessertspoonful in a cup of warm water) induces vomiting in a few minutes: the simplicity and convenience of this method are noteworthy.

The use of salts of heavy metals (copper sulphate, zinc sulphate, etc.) as emetics has been abandoned: locally they are corrosives and if absorbed they are poisonous.

### ANTI-EMETIC DRUGS

It is probable that all procedures which result in vomiting first cause stimulation of the chemoreceptor trigger zone in the medullary surface which then transmits afferent stimuli to the true vomiting centre in the medulla. Certain drugs such as hyoscine hydrobromide and the antihistamines appear to block the passage of these afferent stimuli and thus exert an anti-emetic action.

CHLORPROMAZINE ("Largactil"). Many derivatives of phenothiazine have been used therapeutically and among them is Chlorpromazine Hydrochloride which has a powerful anti-emetic action. Chemically this substance is 10-( $\gamma$ -dimethylamino-propyl)-2-chlorophenothiazine; it is closely related to the antihistamine promethazine ("Phenergan"). It has, however, no significant antihistamine action. Chlorpromazine hydrochloride can prevent the emetic action of apomorphine and may act by depressing the chemoreceptor trigger zone. This substance can suppress nausea and vomiting due to many different causes, for example in carcinomatosis, uræmia, following the use of certain drugs, in pregnancy, and in the postoperative state. It is said to relieve the nausea and vomiting which may follow deep X-ray therapy. Like many other drugs it is reported to relieve intractable hic-cough, but it has no effect on motion sickness. When vomiting is occurring, chlorpromazine hydrochloride is given by intra-muscular injection in a dose of 25-50 mg. which may be repeated 4-hourly. Oral administration is more commonly employed when the drug is being used in order to prevent vomiting. The dose commonly given is 25 mg. three or four times daily. (For the other actions of chlorpromazine see p. 222.)

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DIMENHYDRINATE ("Dramamine") is the 8-chlorotheophyllinate of diphenhydramine. It has been used in the prevention of travel sickness, postoperative nausea and vomiting and for the vertigo of labyrinthine disease (50-100 mg. every 4 hours).

Another compound with similar action and uses is Promethazine Chlorotheophyllinate ("Avomine"): it is given orally in doses of 25 mg.

♂ HYOSCINE. Hyoscine is one of the anticholinergic drugs of the atropine group (p. 679). It deserves mention with the anti-emetics, but with some reservations. Hyoscine, skilfully used, marked a notable advance in our methods of prevention of travel sickness. The condition can be described as a feeling of uneasiness increasing to a state of misery and followed by nausea and (comparatively rarely) by actual vomiting. Hyoscine prevents the onset of this general malaise, and in this sense it can be regarded as an anti-emetic in travel sickness. Once vomiting has developed - either from the effects of motion or from any other cause - hyoscine is of very limited value and it is certainly not the anti-emetic of choice. The successful use of hyoscine calls for careful timing (p. 127).

The pharmacological actions of hyoscine on the central nervous system and on the autonomic nervous system are described elsewhere (p. 126). It may also share to some extent the peculiar anti-emetic action of many of the antihistaminic drugs, but it seems likely that the sedative action of hyoscine on the higher centres is of considerable importance also. This view is supported by people who use hyoscine to suppress completely the malaise of travel sickness and yet find the antihistaminics entirely without effect.

✓ MECLOZINE. Meclozine is the Approved Name for 1-*p*-chlorobenzhydryl-4-*m*-methylbenzylpiperazine, and the dihydrochloride is the proprietary preparation "Ancolan." In doses of 50 mg. twice or thrice daily it is often effective as an anti-emetic in travel sickness. Side-effects are uncommon and if necessary it can be taken on consecutive days during a long sea voyage. The patient who obtains freedom from nausea and vomiting when taking meclozine

enjoys the additional advantages of a drug with a sustained action and no troublesome side-effects.

### ANTACIDS

**INTRODUCTION.** This convenient but uncouth word was invented to describe the main action of a group of substances which, in various ways, diminish the acidity of the gastric secretion. They are remarkably effective in the symptomatic treatment of peptic ulcer: heartburn and epigastric discomfort are usually relieved within 10 minutes, and the sense of well-being is restored. These drugs are also useful in the acute phases of a gastritis even though the patient may be vomiting; gentle lavage with a suitable alkali gives prompt relief of symptoms and accelerates recovery.

Antacids are sometimes divided into two groups, the systemic and the non-systemic. A systemic antacid is one that is soluble, readily absorbed and capable of producing the symptoms and biochemical changes characteristic of the alkalotic state. The non-systemic compounds are not absorbed and therefore do not cause alkalosis. The ideal antacid has the following properties: it is insoluble in water; does not irritate the stomach or the intestine; is neutral in aqueous suspension, but capable of neutralising acid; does not unduly alter the acid-base equilibrium of the body; when taken in any reasonable amount it does not alkalinise the urine—thus avoiding the danger of precipitating crystalline phosphates in the kidney or ureter; it does not cause diarrhoea or constipation, nor does it seriously alter mineral metabolism. In the *British National Formulary* it is stated that the approximate quantities of the individual antacids which are required to neutralise an amount of acid equivalent to the daily output of hydrochloric acid are: magnesium oxide 3 G., aluminium hydroxide 5 G., magnesium carbonate 7 G., calcium carbonate 7 G., magnesium trisilicate 10 G., and sodium bicarbonate 12 G. The neutralising power of bismuth oxycarbonate is negligible.

**MAGNESIUM TRISILICATE.** Magnesium trisilicate is an insoluble tasteless white powder. In the stomach magnesium trisilicate becomes gelatinous in consistence and it is an effective

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adsorbent: it is "non-systemic" in action. The reaction is a complex one, resulting in the formation of hydrated silica and magnesium chloride. The small intestine receives the hydrated silica as a gel and also some of the magnesium trisilicate which has escaped from the stomach unchanged. As they pass through the small intestine the adsorbent effect of both these substances continues. The insoluble residue is eventually passed from the colon and can be recovered from the fæces. The magnesium chloride reacts with the intestinal contents to form magnesium carbonate which is excreted in the fæces; and sodium chloride which is absorbed. After the administration of magnesium trisilicate the initial neutralisation is rapid, utilising 75 per cent of the available magnesium in the first hour. This is followed by a diminishing reaction which is complete in 3-4 hours. This substance is entirely harmless when taken by mouth, and in therapeutic doses it does not affect the motility of the gastrointestinal tract. Large doses may cause diarrhœa, because of the formation of significant amounts of magnesium chloride--a soluble salt which acts as a saline laxative (p. 414). The mode of action of magnesium trisilicate ensures that the gastric contents never become alkaline. The official dose is up to 2 G. (about half a teaspoonful), and the usual regimen is to give this every 2 hours alternating with feeds of milk (2-hourly) while the symptoms of peptic ulcer are acute. When relief of pain occurs the dose may be reduced to 2 G. four times a day, best taken between meals. It has been shown that if the  $pH$  of the stomach contents can be prevented from falling below 4 pain does not usually recur. In practice, however, the patient suffering from peptic ulcer is instructed to take magnesium trisilicate in half-teaspoonful doses as often as may be necessary in order to abolish pain.

**MAGNESIUM OXIDE.** Magnesium oxide (Magnesia) is a white insoluble powder and is used as a "non-systemic" antacid. In the stomach magnesium oxide reacts with hydrochloric acid to form the neutral and soluble salt, magnesium chloride. In the small intestine this salt reacts with sodium bicarbonate to produce carbonate and bicarbonate of magnesium. Magnesium carbonate is almost insoluble and is not absorbed and this salt is wholly

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excreted by the bowel. However, the small quantities of soluble magnesium bicarbonate suffice to cause purgation after repeated administration. Magnesium Oxide is available as "light" or "heavy": the difference is purely physical and is attributable to methods of preparation. Heavy magnesium oxide can be conveniently used in powders whereas light magnesium oxide is more suitable for fluid mixtures. The pharmacological actions are identical; both have an official dose of 0.6-4 G., but to reduce the risk of purgation, 0.3-0.6 G. is the dose commonly used.

MAGNESIUM CARBONATE. Magnesium Carbonate is a white insoluble powder. The "light" and "heavy" salts have identical pharmacological actions. The main difference between magnesium oxide and magnesium carbonate is that the carbonate reacts with the hydrochloric acid in the stomach with the liberation of carbon dioxide, but in doses of 0.6 G. this is not a serious disadvantage. As with magnesia, there is a tendency for magnesium carbonate to cause loose stools.

MAGNESIUM HYDROXIDE. The actions of magnesium hydroxide as an antacid and as a saline laxative are similar to those of magnesia and magnesium carbonate. It is particularly suitable for administration as a suspension in water—described as Cream of Magnesia (Magnesium Hydroxide Mixture, BP)—and this preparation is widely used as a laxative for infants: half a teaspoonful may be given to an infant aged 1 year; the adult dose is 4-16 ml.

All the magnesium salts mentioned above are used in the treatment of peptic ulcer. Other patients without proved ulceration, but suffering from heartburn and flatulent distension associated with gastritis, cholecystitis, hiatus hernia and cirrhosis of the liver, often obtain temporary symptomatic relief from the use of these preparations.

ALUMINIUM HYDROXIDE. Aluminium hydroxide exerts its antacid action by reacting with hydrochloric acid in the stomach to form aluminium chloride. In the intestine the aluminium chloride undergoes a chemical reaction with the alkaline secretions to form basic aluminium salts which are not absorbed. Aluminium hydroxide is thus a "non-systemic" antacid. Aluminium

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compounds are said to inhibit peptic activity because of the inactivation of the enzyme by aluminium ions. Further, the astringent action of aluminium chloride on gastric mucosa is reported to reduce the total volume of gastric secretion. These effects, however, are probably always of subsidiary importance: neutralisation of gastric hydrochloric acid is the principal action. In the intestine the aluminium ion readily combines with phosphate to form an insoluble compound which is not absorbed. Aluminium hydroxide thus decreases the excretion of phosphate in the urine and promotes its elimination in the faeces. Aluminium hydroxide is usually given as a suspension and the *British National Formulary* includes an Aluminium Hydroxide Mixture which contains about 4 per cent w/w of  $\text{Al}_2\text{O}_3$ . The dose is one teaspoonful, diluted with water, taken every four hours or more frequently if necessary. This drug can also be used in tablet form: a tablet (0.3 G.) is available and the dose is one or two tablets. The main use of this antacid is in the treatment of peptic ulceration.

An occasional use of aluminium hydroxide is concerned with attempts to prevent the onset of nephrolithiasis (stone in the kidney). Here the *rationale* is briefly as follows. Stones are apt to form in the kidney when there is a tendency to local deposition of insoluble phosphates in the tubules. One way of diminishing the amount of phosphate passing through the kidney is to prevent its absorption from the bowel. This can be done by giving the patient aluminium hydroxide as this "fixes" phosphate in the intestinal contents in the form of insoluble phosphates of aluminium. Hence giving aluminium hydroxide 0.6 G. with meals thrice daily is a logical procedure in the prevention of nephrolithiasis in patients who have revealed a predisposition to this disease. A diet low in phosphorus is obviously indicated as part of the general management during this treatment. It must be emphasised, however, that other factors may be even more important in individual patients—for example infection and physical abnormalities in the urinary tract.

Occasionally patients receiving aluminium hydroxide develop constipation because of the astringent action of this preparation. In these circumstances, it is usual to give magnesium trisilicate instead of aluminium hydroxide. Alternatively, the two prepara-

tions can be mixed to make a compound powder, and if necessary supplementary doses of magnesium oxide can be given (see above). If bleeding has occurred high up in the alimentary canal, it is inadvisable to use aluminium hydroxide because the combination of this preparation with blood in the lumen of the bowel may result in intestinal obstruction.

**SODIUM BICARBONATE.** Sodium Bicarbonate is a white powder with a characteristic taste. It is widely used as a household remedy for indigestion and is the standard example of a "systemic" antacid. This substance is soluble and easily absorbed, and has an immediate action of short duration in relieving symptoms due to the presence of hydrochloric acid. In the stomach carbon dioxide is liberated as a result of the chemical reaction between hydrochloric acid and the sodium bicarbonate. The eructation of this gas may facilitate the relief of existing flatulent distension of the stomach; and it rarely fails to provide psychological satisfaction for the patient. The complication of alkalosis is by no means unknown when patients indulge in self-medication with large doses of sodium bicarbonate. When large quantities of sodium bicarbonate are absorbed the optimum concentration of extracellular bicarbonate can be maintained only by the renal excretion of bicarbonate, and the urine therefore becomes alkaline. Failure of the renal mechanism to cope with the greatly increased intake of bicarbonate results in alkalosis. Sodium bicarbonate is used to give prompt relief of pain and heartburn associated with peptic ulcer and other disorders of the stomach and duodenum: its effectiveness is beyond dispute—and no harm comes of its occasional use for this purpose—but for a prolonged course of treatment the adsorbents previously mentioned are to be preferred. Sodium bicarbonate is of great therapeutic value in alkalinising the urine at the onset of infections of the urinary tract (pyelonephritis and cystitis). Most of these infections are attributable to *E. coli*: at the onset pain, dysuria and increased frequency of micturition are particularly distressing, and these can be rapidly alleviated by making the urine alkaline. This procedure does not suffice to eradicate the bacterial infection: sulphonamide therapy (p. 505) and occasionally antibiotics (p. 455)

are indispensable for this purpose. Once the urine has become alkaline, the doses of sodium bicarbonate (or other alkalinising salt such as potassium citrate) are reduced, to maintain optimal H-ion concentration of the urine without reducing the constitutional disturbances associated with the alkalotic state.

CALCIUM CARBONATE AND CALCIUM HYDROXIDE. These salts are non-systemic antacids. In the stomach both react with hydrochloric acid to form calcium chloride, and— in the case of calcium carbonate—carbon dioxide is liberated. In the intestine the calcium chloride is largely converted again to insoluble calcium carbonate. This salt resists absorption: it is dispersed in the intestinal contents and in large doses it tends to produce intestinal quiescence and constipation. In combating hyperchlorhydria, these calcium salts are less commonly used than formerly— doubtless because adsorbents are preferred. However, they can be used effectively, especially when combined with magnesium oxide or magnesium carbonate. Further, they are valuable as adjuvants to opium in the symptomatic treatment of diarrhoea.

OTHER ACTIONS OF CALCIUM. The actions of calcium in human metabolism are fully discussed in standard works on physiology and biochemistry. Given an adequate diet and normal mechanisms governing the absorption and excretion of calcium, the need to think in terms of *calcium therapy* is virtually eliminated, for in these circumstances an optimal supply of ionic calcium to meet all contingencies is ensured automatically. Certain physiological effects of calcium are clearly of clinical importance and of potential therapeutic use. For example the actions of Ca and K on the heart are antagonistic to one another and this emerges in the effects of these ions on the myocardium. If the blood calcium is seriously depleted, the characteristic effect of *potassium* becomes apparent and the heart is arrested in diastole. On the other hand an excess of calcium results in arrest of the heart in systole—the state of “calcium rigor”. There are points of similarity between the action of calcium and the action of digitalis on the heart, and the intravenous injection of a full dose of calcium gluconate when a patient is fully digitalised creates a risk of syncope from cardiac arrest in systole.

There is normally no justification for supplementing the dietary calcium to obtain efficient functioning of the myocardium or the



autonomic nervous system, or to anticipate the call for calcium when—in cases of hæmorrhage—clotting of blood occurs at the bleeding point.

Constitutional disorders which result from lack of adequate supplies of available calcium—such as hypocalcæmic tetany and certain diseases involving the tissues of the skeleton—are properly understood only in relation to the physiological principles of calcium metabolism. Again there are many disorders characterised by abnormal deposition of calcium salts in the body tissues. These diseases are primarily the concern of the clinician and the morbid anatomist; but the biochemical mechanisms involved are not without interest to the pharmacologist.

In the following paragraphs a number of pharmaceutical preparations of calcium are listed, and brief reference is made to the clinical conditions in which they are commonly employed. Their therapeutic status should be ascertained by reference to textbooks of medicine and therapeutics.

*Absorption, Fate and Excretion of Calcium.* Calcium is absorbed in the upper part of the intestine, but usually only a small fraction of the ingested calcium is absorbed. A normal person excretes 25–35 per cent of ingested calcium in the urine and the remainder in the faeces. Many calcium salts are insoluble and in this state they are not absorbed. If soluble preparations of calcium are given and if they remain in solution in the upper intestine they may be absorbed when there is a “demand” for calcium by the body tissues; but soluble salts of calcium may be rapidly converted into insoluble salts and soaps and cease to be available because they cannot be absorbed in this state. The absorption of calcium therefore tends to be accelerated by any factors which promote the formation of soluble salts of calcium in the bowel. Thus an acid reaction favours solution of calcium salts; on the other hand the presence of large amounts of unabsorbed fatty acids in the alimentary tract interferes with absorption owing to formation of insoluble calcium soaps. The opportunity for absorption to occur is naturally decreased if there is diarrhœa. Adequate amounts of vitamin D and parathyroid hormone are required for normal calcium metabolism.

**PHARMACOLOGICAL ACTIONS.** *Local Action:* In the normal person, the application of a calcium salt in suitable form and strength to the tissues produces no pharmacological action: the calcium made available is surplus to the needs of the healthy cells.

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Some calcium salts, however, have *physical* properties that give rise to local reactions and these may be more or less severe. Calcium chloride for example is highly deliquescent and if the non-hydrated salt is applied to the tissues it produces considerable irritation. This is apparent after oral administration (nausea and vomiting). Again, if calcium chloride solution is given subcutaneously or intramuscularly there is severe pain and a risk of tissue damage. The drug can be injected intravenously, if it is given *slowly* so that the solution can be diluted in the bloodstream. Alternatively, calcium gluconate, which is free from irritant effects, can be injected intramuscularly or intravenously.

*Preparations and Routes of Administration. Calcium Chloride* (in the hydrated form  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ ) is freely soluble in water. It is valuable in the treatment of hypocalcæmic tetany but must be given orally or intravenously; it is too irritant for subcutaneous or intramuscular injection.

*Calcium Gluconate* contains 9 per cent calcium and is soluble 1 in 5 in boiling water. It can be given orally, intramuscularly or intravenously without causing local irritation. Calcium Gluconate Injection is a 10 per cent solution.

*Calcium Lactate* contains 13 per cent of calcium and it can be given orally or parenterally as an alternative to the gluconate.

*Precipitated Calcium Carbonate* is an insoluble salt. It is not used for producing calcium effects in the body, but is useful in combating gastric hyperchlorhydria (p. 409) and to enhance the effect of opium when this drug is used in the management of diarrhœa.

**THERAPEUTIC USES.** In hypocalcæmic tetany 5-20 ml. of 5 or 10 per cent calcium gluconate is injected *slowly* intravenously. For latent or mild tetany the following preparations of calcium may be given in the doses indicated:

Calcium Chloride—6-8 G. daily (in milk).

Calcium Gluconate—15 G. daily.

Calcium Lactate—4 G. daily.

With preparations other than the chloride Dilute Hydrochloric Acid should be given or alternatively ammonium chloride to promote absorption.

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***Bismuth Carbonate.*** Bismuth carbonate is a white insoluble powder, odourless and tasteless. When taken internally it is said to act as a mild protective by coating the gastro-intestinal tract, but it is difficult to believe that this is ever achieved under clinical conditions. Bismuth carbonate can of course be demonstrated radio-graphically in the gastro-intestinal tract, and the salt may lodge temporarily in an ulcer crater, but this phenomenon is not necessarily of therapeutic significance. As it lies in the bowel, some of the bismuth oxycarbonate is converted into bismuth sulphide, and this results in darkening of the stools. Treatment with bismuth salts may lead to some difficulty in deciding whether a patient has passed a melæna stool. The difficulty should not be exaggerated: the "bismuth" stool is dark grey-black in colour, whereas melæna implies the shiny blackness of tar; and further help is obtained from the proper interpretation of biochemical testing for occult blood. Bismuth oxycarbonate, after repeated administration, has an astringent effect on the lower bowel and causes constipation: this action is occasionally applied therapeutically. Bismuth oxycarbonate was formerly widely used in radio-diagnosis, but it has been displaced by barium sulphate.

The neutralising power of bismuth oxycarbonate is negligible and it has no place in antacid therapy.

### PURGATIVES

**INTRODUCTION.** Purgatives are drugs which are given to accelerate the passage of the intestinal contents. Most of them act by irritation of the mucous membrane of the bowel and in this way peristalsis is stimulated. A few act by reason of their bulkiness in the intestine or by lubrication; their action is relatively mild and they are classed as laxatives and lenitives.

The main indication for the therapeutic use of purgatives is in the treatment of chronic (habitual) constipation. The bowel has been described as "a creature of habit". A normal and well-established rhythm is easily upset by a sudden change of routine (absence from home, emotional crises, etc.): these disorders are self-limiting but may require alleviation by symptomatic treatment. Again the sudden onset of constipation may be one sign among others pointing to acute intestinal obstruction—circumstances which call not for purgatives but for surgical measures. In most cases of chronic constipation, there is rarely intestinal

stasis: the fæcal mass reaches the rectum without undue delay, but there it fails to excite the normal desire for defæcation. As the water in the fæces is absorbed through the rectal mucosa, the rectum and the sigmoid colon gradually become filled with hard fæcal masses (scybala) which are evacuated only with difficulty. It will be understood, therefore, that restoration of the periodic desire to empty the bowel is of primary importance in the treatment of chronic constipation. The absence of this "call to defæcation" is usually the result of neglect in early childhood and adolescence. Advice is commonly sought when the normal habit of regular defæcation has been extinct for as long as ten or even twenty years, and this period has nearly always been devoted to the abuse of purgatives of all kinds. Occasionally, in cases of comparatively short duration, the forbidding of purgatives leads to a spontaneous resumption of regular evacuation, but such cases are rare. In all circumstances it is essential to insist on a real effort on the part of the patient to empty the rectum at a stated time every day. Faults in the diet should be corrected, and in some cases this measure is of considerable value. Thus, the patient should be encouraged to take food which contains a high proportion of indigestible residue—for example green vegetables with the meals every day, and a raw apple in the evening. Extra fluid is usually beneficial—a tumblerful of water before breakfast and at midday; and a pint of beer in the evening often has a mild laxative effect as well as providing additional fluid. Exercise and physiotherapy are often advocated but they are of little value. Patients who are young and agile may be encouraged to perform exercises aiming at improving the power of the muscles of the anterior abdominal wall. These general measures certainly warrant attention, but in practice it is usually found that purgatives of some kind are necessary, at any rate at the beginning of treatment. When the bowels have begun to act regularly, it is sometimes possible to withdraw the purgative. From the clinical viewpoint, pharmaceutical and even pharmacological classifications of the purgatives are of limited value. In the description which follows, the various kinds of laxatives and purgatives have been arranged roughly in ascending order of potency. It must be understood, however, that the actions given are those of average

official doses: in many cases relatively mild action can be obtained from a strongly acting purgative by reducing the dose; and conversely, many laxatives administered in gross overdose produce severe purgation.

1. DRUGS ACTING BY VIRTUE OF THEIR BULK AND INDIGESTIBLE RESIDUE. (1) *Figs, Prunes and Tamarinds* are mild laxatives on account of their high cellulose content. The action is strengthened by the presence of tartrates which are converted into acid tartrates in the bowel; and these acid tartrates act as weak saline purgatives. The cooked fruits may be taken at any time during the day, but are commonly served with breakfast. They are also ingredients in Confection of Senna, where they serve as adjuvant laxatives and give bulk to the preparation. Figs, prunes and tamarinds are valuable in the milder forms of constipation. They cause no ill-effects.

(2) *Agar*. Agar is a tasteless white powder taken in doses of a tablespoonful. In the intestine it absorbs and retains water; it is thus converted into a gel which, by its bulkiness, stimulates peristalsis. Agar is a mild laxative and results in the formation of rather bulky formed stools. In chronic constipation it should be taken several times daily with meals. Proprietary preparations are available in which agar is compounded with liquid paraffin: when the dose is adjusted to the patient's requirements in terms of paraffin, the amount of agar received is trifling and contributes little or nothing to the laxative action.

(3) *Saline Purgatives*. Soluble salts ionise more or less completely in the stomach and intestine, and in the ionised state many of them are absorbed. Some salts, however, dissociate into ions which are absorbed with difficulty. They therefore tend to maintain the osmotic pressure of the intestinal contents and prevent absorption of water. Consequently the chyme and fæces remain excessively fluid and bulky; it is this physical condition which results in increased peristalsis. Magnesium Sulphate is particularly effective because neither the magnesium ion nor the sulphate ion is easily absorbed. The action of Sodium Sulphate depends entirely on the sulphate ion. The phosphate ion and the acid tartrate ion respectively account for the purgative action

## DRUGS ACTING ON THE ALIMENTARY SYSTEM

of Sodium Phosphate and Potassium Acid Tartrate but their effects are relatively weak. For occasional use the saline purgatives are given in full doses on an empty stomach—usually an hour before breakfast. The salt is taken dissolved in about one-third of a tumbler of warm water and is followed by one or two cupfuls of hot tea; in this way the solution passes rapidly into the intestine. Purgation occurs without griping in about one hour with the passage of a bulky watery stool. The saline purgatives are useful when rapid evacuation of the bowel is required, for example to clear the bowel of harmful bacteria or irritant food-stuff. If these salts are given in concentrated solution and fluid intake is restricted, they act much more slowly, say in 2-4 hours, and only after they have withdrawn fluid from the bloodstream; or they may fail altogether. The introduction of a concentrated solution of magnesium sulphate directly into the duodenum elicits contractions of the gall-bladder and lower biliary passages. This action was formerly utilised in the treatment of certain diseases of the liver accompanied by catarrhal obstruction of the bile ducts. Occasionally the treatment is successfully applied to the removal of small gallstones from the common bile duct.

The daily use of a saline purgative may lead to gastric upset and dyspepsia, and it is therefore not the drug of choice for the treatment of chronic constipation. Many patients, however, use the salines in small doses with satisfactory results, taking as little as half a teaspoonful before breakfast every day.

II. LUBRICANTS. Liquid Paraffin is a mineral oil which, when taken by mouth, is not absorbed. If the oil is emulsified a small proportion passes into the lacteals and is stored in the liver. However, most of the paraffin mixes intimately with the food contents of the stomach and intestine when peristaltic and churning movements occur in the alimentary canal. The masses of food-stuff and faeces become coated with a film of oil and this reduces friction with the wall of the intestine. Liquid Paraffin is best given in doses of a dessertspoonful after meals thrice daily, but two or three days elapse before its action becomes established. The stools are formed and have an oily appearance. No griping occurs. Unless the dose is carefully adjusted by the patient, an

excess of oil accumulates in the bowel and trickles down to the anal sphincter where leakage may occur; this is a disadvantage which is serious because it is highly inconvenient to the ambulant patient. Emulsification of the oil or its admixture with agar reduces the risk of leakage. At the same time, if emulsification promotes absorption of this mineral oil and storage in the liver, this is a serious drawback. Liquid paraffin can be used in the treatment of chronic constipation: habituation does not occur, and the preparation is tasteless and inexpensive. Owing to the fact that it takes a few days to act, it is useless in the treatment of constipation when an immediate effect is required. Many people have used liquid paraffin daily for almost a lifetime. Occasionally it has been suspected that in these circumstances the oil may have interfered with nutrition, and that its continuous presence in the colon may have produced polyposis. This danger should not be exaggerated, however, and there is no contra-indication to the use of liquid paraffin daily for a few weeks while steps are taken to restore normal bowel rhythm.

III. IRRITANTS. (I) *Castor Oil*. When taken by mouth castor oil is unchanged in the stomach. In the duodenum, being a vegetable oil, it is acted upon by lipase and broken down into ricinoleic acid and glycerin. The acid is neutralised to form soaps—sodium and potassium ricinoleates—which are mildly irritating to the intestine. A considerable proportion of a therapeutic dose of castor oil escapes saponification and the unchanged oil acts as a lubricant. As the irritant ricinoleates are liberated early and high up in the small intestine, increased peristalsis develops an hour or two after the administration of the oil; purgation usually occurs in 4–6 hours and the stool is soft, unformed and oily in appearance. Severe griping is not common. Subsequently the bowel becomes quiescent for a longer period than is usual after other purgatives, and constipation may last several days. For this reason, castor oil is to be avoided in the treatment of chronic constipation. The main indication for its use is where rapid and thorough emptying of the bowel is needed with a minimum of constitutional upset. It is well tolerated by infants and old people. Many patients object to the smell and taste of

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castor oil. It is more easily swallowed if taken warm. Alternatively it may be emulsified with gum acacia and flavoured with syrup of ginger. Another way of giving the oil is to float it on concentrated natural lemonade. The dose of the oil for an adult is about a tablespoonful, but, if emulsified rather larger doses are necessary. Obstetricians administer doses of about one ounce of castor oil to pregnant women at full term in order to precipitate the onset of labour.

(2) *Sulphur*. Like castor oil, sulphur is inert in the stomach and only becomes active in the bowel. On reaching the intestine small quantities of sodium and potassium sulphides are formed slowly. The alkaline sulphides are extremely irritating but in the small amounts that form in the bowel only mild stimulation occurs. Purgation results after about 10 hours and griping is negligible. The stools are soft and formed—but very offensive owing to the presence of sulphuretted hydrogen. The only objection to the use of sulphur as a laxative is the offensive smell which it gives to the motions; and as sulphides are also excreted by the skin and by the lungs, there is a constant odour of sulphur which is highly disagreeable. Sulphur is therefore not used in the treatment of chronic constipation. Because of its mild action, however, it is of special value for occasional purgation in old people and in children. It is also useful when it is particularly important to reduce to a minimum the abdominal discomfort that may accompany purgation—as, for example, in the presence of hæmorrhoids or during menstruation. The Confection of Sulphur is a convenient preparation; another—old-fashioned but fairly widely used—is Compound Liquorice Powder, in which sulphur re-enforces the action of senna, and liquorice is merely a flavouring agent.

(3) *Phenolphthalein*. Phenolphthalein is a tasteless, white powder insoluble in water. It is unaffected by the gastric juice. In the intestine, however, it is converted into soluble alkaline salts which irritate the mucous membrane and stimulate peristalsis. Purgation occurs after about 6 hours; the stool is soft and formed. There is rarely much griping. A part of the phenolphthaleinates is absorbed: some is excreted in the bile and thus finds its way back to the intestine, with the result that purgation may occur twice or even three times following one dose of the drug; some appears in the urine which turns bright pink in colour if it is



alkaline. Toxic effects from phenolphthalein are rare, but occasionally the drug produces an itching skin eruption characteristically with macules of a dusky purplish colour. The fact that the bowels may move several times following a single administration of phenolphthalein is not regarded as a disadvantage by the majority of patients. It is possible, however, that the effect upon the liver and gall bladder may be harmful when phenolphthalein is used daily. The drug is widely employed as a household remedy, especially in the form of proprietary preparations; it is often compounded in a chocolate base but this is justifiable only on commercial grounds. A Tablet of Phenolphthalein is available containing 120 mg. and the usual dose is one or two tablets.

(4) *Mercury*. Metallic mercury—if finely divided—and also the insoluble subchloride of mercury (calomel) were once much used as purgatives. The action of the metal will be considered first. In the stomach small quantities of mercury dissolve in the hydrochloric acid but the amount of chlorides formed is insignificant. In the intestine a small proportion of the finely divided metal is slowly converted to soluble proteinates. These organic compounds irritate the intestinal mucous membrane and produce purgation in about 6 hours. Griping is common. The stool may be soft and formed; and it is often stained green by unchanged bile. Not infrequently, however, ordinary doses of the mercurial purgatives produce a more violent effect: griping is severe and is followed by the passage of several liquid motions. The bilious appearance of the motions is attributable to the antiseptic action of mercury proteinate in the bowel, inhibiting bacterial activity which is normally responsible for the conversion of biliverdin to stercobilin. There is no increase in the volume of bile secreted, and mercury is not therefore a true cholagogue.

Some of the mercury is absorbed in the form of the proteinate. This fraction is excreted by the kidney. Here, by its action on the tubular epithelium, it inhibits the normal reabsorption of sodium and thus acts as a diuretic. This side-effect of the inorganic preparations of mercury has been exploited by the introduction of synthetic organic mercurials such as mersalyl (p. 31) which are of great therapeutic importance. When mercury is used only for its purgative action, however, the fact that some of the metal is absorbed is a serious disadvantage. The absorbed mercury disappears from the tissues very slowly; hence if mercurial preparations are used daily

or even at intervals of a few days cumulation occurs and toxic effects may appear. In practice, therefore, mercury is used only as an occasional purgative and is contra-indicated in the management of chronic constipation. As already mentioned, the proteinate of mercury acts as an antiseptic in the bowel. The use of mercurial purgatives was therefore justified when the objective was to empty the lower bowel and simultaneously to combat putrefactive changes in the intestinal contents. The advent of sulphonamides, however, quickly rendered this form of therapy obsolete. Again, the use of mercurials as laxatives for infants is no longer recommended, because such vigorous treatment often causes serious dehydration; and the use of mercury appears to be an important factor in the pathogenesis of some cases of polyneuritic erythrœdema ("pink disease").

(5) *The Anthracene Group.* This group includes rhubarb, cascara sagrada, senna and aloë. Their active principles are glycosides which, on hydrolysis, release chrysophanic acid, emodin and other principles chemically related to anthracene. These active principles are slowly liberated as the crude drugs pass down the alimentary canal. After absorption they are re-excreted from the blood stream into the colon—where they produce their irritant effect: this has been demonstrated experimentally by injecting the active principles intravenously and producing rapid purgation. When they are used therapeutically, the anthracene preparations are taken in the late evening—before going to bed—and the bowels move about breakfast time on the following morning. Although the severity of the purgative action shows some correlation with the particular anthracene selected, its dose and the time of administration, the optimum conditions for use in the individual patient can be determined only by observation and adjustment. Some of the difficulties can be attributed to variation in strength of official preparations, but recent work on the standardisation of senna has simplified this part of the problem. The use of purgatives in clinical practice, however, illustrates that in biological experiments there are many variables—including individual susceptibility to the action of a drug—and these factors set a limited value on the "average experience". Usually purgation occurs only once, but aloë often causes 2 or 3 evacuations—and this points to repeated circulation of the glycosides by absorption

and re-excretion before their final elimination or destruction. The stool is usually soft and formed, but unformed or even liquid stools sometimes occur. Some of the glycosidal derivatives in senna and rhubarb sometimes cause a golden-yellow colouring of the stools; excretion of these substances by the kidney results in coloration of the urine—yellow if it is acid and red if alkaline. Rhubarb contains rheotannic acid which is said to cause noticeable constipation after purgation has occurred, but this action is rarely of any importance in practice.

The anthracene drugs are of special value in the treatment of chronic constipation as they do not cause *habituation*; when given over a prolonged period, it is seldom necessary to increase the dose in order to produce a satisfactory result. The fact that these drugs act only on the large intestine is also an advantage where daily administration is needed often over a period of months. The only important drawback is the tendency of the anthracene purgatives to cause griping. An attempt is made to overcome this by the liberal use of carminatives in most of the official and BPC preparations of these drugs. Cascara Sagrada is bitter, but it can be taken in the form of the Liquid Extract or in the more palatable preparation known as the Elixir; both these liquid preparations have a dose of 2–4 ml.; alternatively cascara may be taken as a pill made from the Dry Extract. Aloe is intensely bitter and cannot be tolerated in any form other than the pill, with or without a carminative. Much pharmaceutical research and ingenuity has been directed to making a large number of preparations of the anthracene purgatives. Here, however, as with other forms of therapy, the doctor's objective is the skilful use of the smallest selection of preparations which will meet the needs of his patients.

(6) *Drastic Purgatives.* (Jalap, Ipomœa, Colocynth and Podo-phyllum.) The action of these drugs depends upon the presence of glycosidal resins. The glycosides are liberated in the upper intestine and are then hydrolysed yielding glucose, and irritant acids which stimulate peristalsis. These chemical changes occur only in the presence of bile and the rate at which the decomposition proceeds determines the time taken for the drugs to cause purgation. Jalap and Ipomœa (Scammony) act in about 4 hours; Colocynth takes about 6–8 hours, and Podophyllum is remarkable in that it takes as

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long as 16 hours to produce evacuation. The rapidly-acting members of the group result in liquid stools because the intestinal contents are hurried along so quickly that re-absorption of water from the bowel is prevented; also there is often excessive secretion of mucus from the intestinal glands as a result of the irritant effect of the drugs upon the mucous membrane, and this increases the amount of fluid in the motion. When they are given in large doses, the purgatives of the jalap group cause marked irritation and congestion of the intestinal mucosa and evacuation is accompanied by *straining*; strictly, this is what is implied by the term "drastic" in the present context. The alternative description—"hydragogue"—refers to the tendency for these drugs to cause serious loss of water in the stools and consequent dehydration of the tissues. In average official doses, however, colocynth and podophyllum produce soft, formed or unformed stools. All the drugs of the jalap series cause griping, and carminatives are added to most of the official preparations to alleviate the discomfort: relief of spasm in the bowel wall may be achieved by the simultaneous use of anticholinergic drugs of the atropine group or (with less hope of success) by adding volatile oils. Jalap and ipomœa are used when a rapid and thorough evacuation of the bowel is desired. Their dehydrating effect was formerly applied therapeutically in order to diminish the quantity of free fluid in the tissues, for example in renal dropsy, in reducing the painful congestion of inflammatory lesions, and (in special circumstances) to relieve tension in engorged breasts during lactation. In countries where it is possible to use selective therapeutic procedures, these uses of purgatives are regarded as obsolete and not free from dangers of water depletion and loss of electrolytes.

(7) *Croton Oil*. This drug is important to the pharmacologist only inasmuch as it reveals the recklessness (sometimes called "the heroic attitude") of a former generation of practitioners. One drop of croton oil suffices to cause violent purgation. Irritation is so intense that the effect must be regarded as a chemical enteritis: the frequent evacuation of "rice-water" stools with blood, mucus and even fragments of mucous membrane, and serious constitutional upset (dehydration and collapse) serve to show that croton oil was never properly classified as a therapeutic agent. The preparation was deleted from the BPC 1954. It is obsolete.

IV. MISCELLANEOUS PROCEDURES. In addition to the purgatives described above, a number of drugs may conveniently be

mentioned here in connection with their action in increasing peristalsis.

(1) *Neuromuscular Stimulants*. The actions of these drugs are described elsewhere (see index). Although all of them may cause increased peristalsis they are never used in the treatment of chronic constipation. When constipation is a troublesome side-effect of ganglion-blocking agents used in arterial hypertension relief is often obtained from small doses of pilocarpine or physostigmine. Posterior pituitary extract can be used as an intestinal carminative leading to the expulsion of flatus: evacuation of faecal contents of the colon usually follows in 2-3 hours.

(2) *Strychnine* was formerly used as an adjuvant in purgative preparations. It was thought that as this alkaloid increases the sensitiveness of spinal reflexes (tendon jerks) it might act similarly in relation to reflex mechanisms in the bowel wall. There is no evidence to support this view as far as therapeutic doses of strychnine are concerned. The use of strychnine adds an unnecessary and useless complication to the management of constipation.

(3) *Rectal Irritants*. Glycerin introduced into the rectum, for example as a suppository, irritates the rectal mucous membrane by its hygroscopic action (p. 612). Peristaltic movements then develop in the descending and pelvic colon and purgation results usually within 30 minutes.

(4) An *Enema* used in order to empty the lower bowel is called "an evacuant enema". Its action depends mainly on its bulk (about one pint of warm water). Irritant substances should not be added: they are rarely necessary, and they may cause discomfort which is naturally resented by the patient. For its lubricant properties, a little toilet soap may be added to the water (enough soap to make the water froth). Although the stimulus is applied mainly to the rectum peristaltic activity occurs in the descending and sigmoid colon, and evacuation of this part of the large bowel is fairly complete.

#### ASTRINGENTS

The word astringent implies a "drawing together" of the tissues. Substances which act as astringents combine with protein to form proteinates. This action is readily demonstrated *in vitro*.

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On the living tissues the protcinatc or coagulum is formed from the superficial cells: thus a film of relatively insensitive material is laid down and it affords a degree of physical protection to the deeper tissues. Mucous secretion and also the exudate that "weeps" from an inflamed surface are similarly coagulated by astringents. These drugs fall into two classes: 1. Soluble salts of the "heavy metals", especially lead subacetate, zinc sulphate, and alum. 2. Tannic acid and the vegetable substances which contain tannic acid. The potency of astringents depends on a number of factors: if a metallic salt is freely soluble in water and ionises readily, and if *both* ions react with protein, the salt is likely to be a powerful astringent. Again, certain metallic ions are inherently more astringent than others: mercuric, ferric and cupric ions are at the "strong" end of the scale; zinc, lead and aluminium are relatively weak. The acidic radicles can be similarly classified: nitrates and chlorides are strong astringents whereas sulphates and acetates are weak. When an astringent is being selected for therapeutic use, these considerations need to be borne in mind. Thus the combination of powerful ions which gives mercuric chloride provides a preparation which is capable of producing an intense astringent effect which is not confined to the surface epithelium; it penetrates deeply and its destructive effects may cause ulceration—hence its synonym "corrosive sublimate". At the other extreme there is lead subacetate which, applied in solution (Goulard's Lotion), has an extremely mild and superficial astringent effect. Other preparations such as copper sulphate, silver nitrate and alum, occupy an intermediate position. The selection of the appropriate astringent for a particular therapeutic purpose is a matter of clinical judgment, and recommendations based on clinical experience are obtainable in books of reference (see Martindale: *The Extra Pharmacopœia*, Vol. 1). It must be remembered also that a preparation which in ordinary circumstances acts as an astringent can produce mild corrosive effects if applied repeatedly or in excessive concentration. Conversely, a single application of a solution of a corrosive salt in extremely dilute solution may act as a mild astringent.

The oral administration of metallic salts is practically obsolete. An exception is the use of preparations of iron in anæmia. Here it

is important to remember that although astringency is slight if ferrous salts are used, gastric irritation with nausea and vomiting may occur if iron medicines are given to fasting patients. Again the tannic acid and tannates of strong "stewed" tea may cause dyspeptic symptoms. When tannic acid is liberated into the bowel its effect is thought to be to diminish the sensitiveness of the mucosa and to diminish secretion. This treatment is therefore likely to cause constipation; and preparations such as Extract of *Krameria* were therefore used in the symptomatic management of diarrhœa. It was often difficult to assess their effect because they were rarely given except with opium—which powerfully inhibits peristalsis. They were probably of some value, but the use of astringents in bowel infections has been rendered obsolete by the introduction of sulphonamides and antibiotics. Tannic acid also enjoyed short-lived popularity in the treatment of burns. A solution of the astringent was sprayed on the damaged tissues which were thus coagulated or "tanned", the object being mainly to prevent the loss of body fluid. This treatment was abandoned because of the frequent formation of abscesses under the brown-black pellicle; and there were occasional cases of liver damage following absorption of tannic acid from large areas of granulation tissue, but it is unlikely that the tannic acid—which is firmly fixed in the superficial tissues—accounts for remote toxic effects.

### DEMULCENTS

**INTRODUCTION.** Most of the external surfaces of the body are protected and lubricated by natural secretions. Deficiency of these secretions and consequent "dryness" of mucous membranes is a common occurrence in many diseases. The immediate effects may be disagreeable for the patient and, even more important, the abnormal state of the tissues often predisposes to infection with local and constitutional complications. Thus, there are good reasons for the use of local applications which have physical properties similar to those of the natural secretions. There is a large number of drugs which serve this purpose when they have been suitably prepared by the pharmacist. Although they differ widely in their botanical and chemical characters they have in

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common a demulcent effect on the superficial tissues of the body: they are mucilaginous preparations which exert a soothing action on inflamed or irritated surfaces.

A number of these drugs are mentioned below and brief reference is made to certain properties which are of importance to clinicians and pharmacists. Additional information about these drugs is available in Appendix 4.

ACACIA is a gummy exudation from the stem of the acacia tree. Acacia is a tasteless white powder, soluble in water, and it has a bland "mucilaginous" taste. When it is suitably prepared it can be used as a protective on mucous membranes; a useful preparation for application to mucosæ and to the skin is a mixture of equal parts of this mucilage and glycerin. Gums such as acacia are widely employed in pharmacy: they act as *emulsifying agents* and thus facilitate the administration of oils. Acacia is also a *suspending agent* but is less satisfactory than tragacanth (see below): the mucilage is added to fluid mixtures when it is necessary to hold in suspension powdered drugs which are insoluble in water.

TRAGACANTH is a gummy exudation obtained by incising the stems of a plant—*Astragalus gummifer*. The pharmaceutical preparation is a tasteless white powder. In water it swells to form a gelatinous mass which is *almost insoluble*. The preparations commonly employed are the Mucilage and the Compound Powder (Appendix III). Tragacanth is used as a suspending agent and an adhesive powder for dentures. Like acacia it can be mixed with glycerin to make pastes for the treatment of skin diseases.

GELATIN is the gelatinous, translucent substance obtained by extracting animal tissues (bones, skin, tendons and ligaments) with boiling water. Chemically it is a partly hydrolysed protein. It is available in sheets, shredded, or as a dried whitish powder which is almost tasteless. In cold water it swells and imbibes 5–10 times its weight of water. It is soluble in hot water and forms a gel on cooling; it is also soluble in a mixture of glycerin and water.

Gelatin in a paste with glycerin and water forms a protective



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basis in which to incorporate antiseptics such as resorcin or astringents such as zinc salts in the treatment of skin diseases.

Gelatin capsules (thin-walled cylindrical containers) are used as a means of administering drugs which would otherwise be unpleasant to take. Plain gelatin capsules dissolve in the stomach and release their contents in a few minutes. If it is desired to delay the digestion of the capsule it can be made resistant to the gastric juice by treating it with stearic acid or keratin solution or by hardening it in formalin.

Gelatin is a demulcent and pastilles can be made using gelatin, glycerin and water: flavouring agents and colouring matter are commonly added. If in addition to the demulcent effect, a topical astringent or antiseptic action is needed, appropriate medicaments are incorporated into the pastille. In the glycerin suppository gelatin acts as the "vehicle": it gives this pharmaceutical preparation the suitable shape and consistence for insertion into the rectum. When the gelatin melts the undiluted glycerin is released, and because this is hygroscopic it sets up gentle irritation of the rectal mucosa resulting in evacuation of the bowel.

### FLAVOURING AGENTS AND CARMINATIVES (INCLUDING VOLATILE OILS)

Flavouring agents are aromatic substances used to impart an agreeable odour and taste to pharmaceutical preparations. Carminatives are drugs containing volatile oils—or other volatile substances such as alcohol, chloroform, etc.—which promote relaxation of involuntary muscle of stomach and intestine, thus facilitating the expulsion of gas from the alimentary canal and relieving flatulence and colic.

Volatile oils act both as flavouring agents and carminatives. Their synonym "essential oils" serves as a reminder that many of them have culinary uses as essences (vanilla, clove, lemon, etc.). They are obtained from plants and differ chemically and physically from the non-volatile fats and fixed oils, some of which are used as foods (olive oil, butter fat, etc.). The volatile oils are generally clear, colourless fluids with a strong perfume. They are only slightly soluble in water, but this suffices to provide "aromatic waters" (peppermint water, dill water, etc.) which make elegant

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vehicles for drugs given in solution. Although the essential oils have an official dose (0.06-0.2 ml.) they are rarely or never given except when suitably dispersed—in water, chalk, etc. Large doses are poisonous: they depress the central nervous system, causing drowsiness passing on to coma and paralysis of the medullary centres. Toxic doses also cause acute nephritis with suppression of urine and uræmia.

When applied to the skin volatile oils act as irritants. They are soluble in fats and therefore they can penetrate the skin. Thus they stimulate sensory nerve endings and produce a sense of warmth and tingling. If these cutaneous sensations are sufficiently powerful they take precedence in the patient's consciousness over discomfort arising from deep-seated disease. This is essentially the objective when irritants are deliberately applied to the skin, and because of their indirect effects they are called *counter-irritants*. The production of mild skin pain is all-important; the accompanying flushing of the skin has a negligible therapeutic significance. Certain of the volatile oils therefore such as turpentine, camphor, menthol and methyl salicylate are used as counter-irritants.

The volatile oils all possess antiseptic properties and Clove Oil is thus employed in dentistry. Small doses (one drop) in dilute solution given by mouth have a mild irritant action and cause a sense of heat in the epigastrium. The eructation of gas from the stomach is also facilitated: this *carminative action* probably depends on the ability of volatile oils to cause relaxation of plain muscle, and when this occurs at the cardiac end of the stomach voluntary movements directed to belching are usually more successful.

Preparations of peppermint and ginger are popular among adults. Dill Water sweetened with sugar and glycerin is traditionally used—often with striking success—to relieve “windy spasms” in infants. Volatile oils are conveniently administered in alcoholic solution: these preparations are the official *spirits*. The carminative effect of brandy is partly due to its alcohol content and partly to the action of volatile higher esters.

By irritating the gastric mucosa volatile oils may cause some reflex quickening of respiration, tachycardia and rise in blood

pressure for a brief period. They are, for this reason, given as reflex restoratives in syncope, along with more potent irritants, e.g. Spirit of Camphor. Volatile oils are partly excreted in the breath, and it has been assumed that they increase the output of sputum (expectorants) and possess antiseptic actions in the lungs. These actions—if they occur at all—are of no therapeutic importance *in man*, though it may be justifiable to use volatile oils in “cough medicines” as flavouring agents (Appendix III).

**LIQUORICE** (*Glycyrrhiza*). The prepared root of the liquorice plant is a pale-yellow powder. It has a sweet and agreeable taste and is used in medicine as a *flavouring agent*. The student should not confuse it with Compound Liquorice Powder—which is a laxative flavoured with liquorice.

The special merit of liquorice as a flavouring agent is that its characteristic flavour makes certain medicines tolerable even though their taste is not completely eliminated. This applies to saline preparations such as ammonium chloride and bitter substances such as aloe. About a teaspoonful (4 ml.) of the Liquid Extract of Liquorice is added to each dose of a fluid mixture.

It is interesting to note that *prolonged* administration of liquorice has a similar action to that of the salt-retaining steroids of the suprarenal glands. The biochemical and clinical aspects of this subject are dealt with in the appropriate journals.

#### SWEETENING AGENTS

The most important sweetening agents are the sugars, though liquorice, glycerin and saccharin are also used. Ordinary sucrose (cane sugar, beet sugar) fulfils most requirements, but where an easily assimilable carbohydrate is needed—especially in febrile illnesses—glucose is often preferred because it is not excessively sweet. Glucose is added to the patient's drinks; when intravenous infusion is indicated, however, the pure substance Dextrose must be used. Lactose is not a very efficient sweetening agent, but it has special pharmaceutical uses which are mentioned below. The sweetest of all the sugars is *lævulose*, but it is rarely used except in the *lævulose* tolerance test of liver function.

## DRUGS ACTING ON THE ALIMENTARY SYSTEM

SUCROSE crystallised from the juice of the sugar cane or sugar beet and also preparations of sucrose are used chiefly as sweetening agents and as diluents for other drugs. Syrup (sucrose in distilled water) is also a demulcent. Sucrose was formerly injected intravenously in 50 per cent solution as a diuretic. This use, however, has been abandoned because sucrose (unlike dextrose) has harmful effects on the tissues when it remains in direct contact with the body cells. Simple Syrup can be made more palatable by the addition of fruit juice such as Raspberry Syrup or Syrup of Orange.

LACTOSE or milk-sugar is a crystallised sugar obtained from whey of milk. As it is non-hygroscopic it is commonly used as a diluent to give bulk to potent drugs administered as powder. It can also be used to sweeten cow's milk suitably diluted for artificially-fed infants, but sucrose is often found to be satisfactory; and excessive amounts of lactose cause diarrhœa. Lactose has been given with *B. acidophilus* to alter the intestinal bacterial flora in chronic diarrhœa, but the value of this treatment is open to question and it is an expensive form of therapy.

DEXTROSE (*d*-glucose) commonly called "glucose" is prepared by hydrolysis of starch. It is easily assimilable, less cloying than sucrose when taken frequently, and is often added to the patient's fruit drinks in acute infective fevers. It is also given to infants with persistent vomiting (especially if suffering from acidosis) and it is used as a protective to the liver in the various types of hepatitis. The administration of dextrose to supply energy is of particular importance in patients suffering from renal failure with anuria: the sugar is utilised by the body tissues without further demands on renal function. If the patient has difficulty in swallowing, food is given by intragastric drip and sugar (cane sugar, glucose or dextrose) is commonly added to the feeds.

The Injection of Dextrose is a 5 per cent sterile solution of dextrose in water. It is intended for intravenous infusion; if carefully supervised it can also be given effectively by rectal drip. The intravenous injection of dextrose is normally given slowly by the drip technique. It can, however, be given rapidly as an emergency restorative in the treatment of shock and of any sudden blood loss,

pending the infusion of blood or plasma. Intravenous infusion of dextrose solution is the standard method for providing food and for maintaining hydration of the body tissues in renal failure, in diseases associated with persistent vomiting, in liver failure and following surgical operations. Dextrose administration is sometimes used to ensure an adequate reserve of carbohydrate prior to prolonged operations, especially if there is any suspicion of incipient hepatic failure. In poisoning by organic arsenicals, chloroform or carbon tetrachloride, sugar by mouth is supplemented by intravenous injection of dextrose to protect the liver by building up its glycogen content. In the treatment of hypoglycæmia due to over-dosage of insulin or from any other cause, for example Sheehan's syndrome, dextrose must be given orally—or intravenously if the condition of the patient warrants it. In large doses dextrose given intravenously acts as a diuretic: when the renal threshold is persistently exceeded the glucose which escapes reabsorption in the proximal tubule of the kidney exerts an osmotic effect and thus promotes a diuresis. Sustained hyperglycæmia should therefore be avoided as it may aggravate the state of dehydration which the physician is trying to relieve. On the other hand, if temporary dehydration of the tissues is the objective—as in cases of increased intracranial pressure—this may be achieved by slowly injecting 20 ml. of a 50 per cent solution of dextrose. The diuretic and dehydrating effects of dextrose are not seen (except in diabetics) when it is given by mouth.

The pharmacist uses Syrup of Liquid Glucose as an excipient for making pills. Glucose is also used as a reducing agent when ferrous salts of iron are dispensed in solution: the tendency of the ferrous salt to be oxidised to the ferric state is thus retarded.

SACCHARIN is the anhydride of *orthosulphonamide-benzoic* acid. Its sodium salt is commonly employed because it is soluble. This substance is used as a sugar substitute by diabetics and by obese patients on a reducing diet. It is intensely sweet, 300–500 times sweeter than cane sugar. It is not a food and it is excreted unchanged in the urine. Although it is not a toxic substance saccharin occasionally produces allergic reactions in the form of skin rashes, nausea and vomiting.

# CHAPTER 15

## ANTIBACTERIAL AGENTS

### INTRODUCTION

MANY procedures connected with food preservation—the use of heat, cold, salt, spices, impregnation with smoke—were used empirically for thousands of years before man became aware of the existence of micro-organisms. Modern concepts of bacteriology stem from the pioneer work of Pasteur, Metchnikoff, Koch, Lister and many others who flourished in the second half of the 19th century. Certain bacteria were identified as the essential causes of a number of diseases, and the new science of bacteriology grew rapidly.

Not the least important objective of the bacteriologist is to define the functions of micro-organisms in their respective environments. It has thus been possible to identify certain bacterial populations (or “flora”) that are compatible with health; indeed they are sometimes essential to health. The reasons for the existence of bacteria and the role they play in relation to the life and fate of the higher animals (including man) are aspects of ecology too complex for discussion here. There is a great deal of relevant information on such subjects as these: the resourcefulness of the human body in defending itself against pathogenic organisms; the futility of trying to rid certain tissues of their normal bacterial flora; and the fact that resorting to chemical disinfectants in an attempt to achieve prolonged sterilisation of the skin or the alimentary canal is not only useless but may be harmful—by injuring the tissue cells and thus impairing their natural defence mechanisms. The medical practitioner—concerned as he is with the relief of anxiety and the prevention of disability—may hope to convey information of this kind to his patients, when it is obvious that they harbour very primitive ideas about the functions of bacteria; and not infrequently the doctor finds it necessary to review the claims of vendors of disinfectants in the light of certain broad principles which embrace the science of bacteriology and of pharmacology.

There are of course circumstances that disturb the normal bacterial flora in man. These events include accidental encounters with pathogenic organisms which (in a variety of ways) contrive to break through the protective barriers. The course of events—both local and constitutional—that may follow receive detailed study and classification in standard works on pathology and bacteriology.

Repeated confirmation of the importance of infection as a cause of disease and disability led to unremitting activity in the search for chemical substances capable of destroying micro-organisms in all situations. Over a period of about a hundred years a great deal of exact information has been placed on record about disinfectants, antiseptics and parasitocides of various kinds. Many of these publications are invaluable for the effective practice of hygiene and therapeutics. Research, however, has served also to reveal the limitations of chemical agents of this type when they are used to inhibit or to terminate bacterial activity in a patient's tissues. It is sometimes easy to attack a pathogenic organism such as a fungus which may be growing on the surface of the skin or on a mucous membrane. One or two applications of an antiseptic (for example Solution of Iodine) may kill the fungus outright and effect a complete and permanent cure. Such favourable conditions for eradicating infection or infestation are, however, exceptional. Very often the micro-organisms are buried in the deeper tissues—for example beneath the base of an ulcer crater—and may not be within reach of a disinfectant applied locally. Again the potency of the drug may be greatly reduced by the effect of serum or pus in the wound. If an attempt is made to counter such effects by increasing the concentration of the antiseptic, one result may be to precipitate a state of chemical inflammation at the site and in the surrounding healthy tissues, and thus interfere with the efficiency of natural protective mechanisms which are ultimately indispensable to tissue healing and repair. All extraneous chemical substances applied repeatedly to living tissues with the object of "reacting" with the cytoplasm of micro-organisms almost invariably create a state of sensitisation: sooner or later, normal tissues which are under repeated chemical assault, tend to respond with an inflammatory reaction, and this

may well prove to be more disabling than the original infective lesion. A further risk which is incurred when large quantities of a disinfectant are applied to the body surface is that toxic effects may develop elsewhere following absorption—for example in the nervous system or in the channels of excretion (kidney, etc.).

For a variety of reasons, therefore, medical practitioners have ceased to depend greatly on topical therapy with chemical disinfectants which owe their effects to a direct action on the cytoplasm of bacteria. The *systemic* use of sulphonamides and antibiotics marked an important advance towards the ideal in the management of infections of many kinds. When an antibacterial action is achieved by drugs (or their degradation products) carried by the blood stream into the tissue fluids a therapeutic principle of capital importance is being applied. This concept of therapy, however, is by no means new. It dates from Ehrlich's attempts (at the beginning of the century) to devise methods calculated to sterilise man's tissues of pathogens by introducing into the circulation a suitable chemical substance: he paid special attention to the cure of syphilis by means of organic arsenicals. It is interesting to observe that notwithstanding what has been said about the serious limitations of topical therapy with chemical disinfectants, many of the newer antibiotics (p. 469) can in fact be used in this way, and they are often of much greater clinical value than the older series of preparations which are mentioned in the following pages. It is true that there is ample scope for exercising discrimination in the selection of new drugs for local application to skin and mucous membranes. Penicillin and the sulphonamides were at one time used freely on infected superficial tissues. To a large extent this practice has now been abandoned because these preparations often produce sensitisation reactions. It will be noted (Chapter 15) that among the antibiotics which are now used to combat infections on the body surface many are used exclusively for this purpose.



## Antibiotics

### PENICILLINS

The discovery of penicillin in 1928 by Fleming and its subsequent development for clinical use by Florey and his co-workers are matters of medical history that have become a part of common knowledge. Penicillin is still the most important antibiotic; it has retained its pre-eminence despite the many antibacterial agents now available. This derives from its potent bactericidal action against the organisms responsible for the common infections in man and its relative non-toxicity even if very large doses are given. The term penicillin is now used generically to include the various preparations used in therapeutics.

#### SOURCES AND CHEMISTRY

Penicillin is produced by the moulds *Penicillium notatum* and *Penicillium chrysogenum* and although synthesis has been achieved, culture of the mould on a large scale is the method of commercial production. Penicillins are organic acids with the same basic chemical structure consisting of a fused thiazolidine and  $\beta$ -lactam ring. A number of acids are produced during the growth of the mould, differing only in the side-chain attached to the  $\beta$ -lactam ring. Others have been made biosynthetically by the addition of various chemicals to the culture medium and by this means a large number of different penicillins have been isolated. In therapeutics, however, only two are commonly employed—Benzylpenicillin (Penicillin G) in which a phenylacetamido side-chain is attached to the  $\beta$ -lactam ring, and Phenoxymethylpenicillin in which the side-chain is a phenoxyacetamido group. Other acids have been used, for example Penicillin O, and these are briefly mentioned on p. 442. The various salts of benzylpenicillin employed in therapeutics are detailed on p. 440.

#### ANTIBACTERIAL ACTIONS

Penicillin is a narrow spectrum antibiotic, that is to say it is effective against relatively few species of bacteria compared with, for example, the tetracyclines which have a much wider range of

activity. Gram-+ve and Gram--ve cocci and some Gram-+ve bacilli are included among the most sensitive organisms, but Gram--ve bacilli are generally resistant to its action. *Leptospira*, *Treponema* and a few large viruses are also susceptible. It should be noted that although penicillin is an effective bactericidal agent against organisms such as *C. diphtheriae* and *Cl. welchii*, it is not curative in diphtheria and gas-gangrene because the powerful toxins produced by these organisms are not influenced by penicillin. In these diseases early treatment with adequate doses of specific antitoxin is essential. The clinical conditions in which penicillin is the treatment of choice are discussed in the section on therapeutic uses. Penicillin inhibits the growth of organisms in very low concentrations, but higher concentrations of the drug (easily attained in man) are bactericidal. It exerts its action on young actively-growing organisms and indeed the effect is initiated before cell division has occurred, provided the medium is favourable for rapid organismal growth. On the other hand, against organisms in the resting phase it is ineffective. It appears that once a critical level of penicillin is reached bactericidal action proceeds at a constant rate and increasing concentrations of penicillin do not hasten the rate of destruction of the organisms. Indeed, with certain organisms, for example staphylococcus tested *in vitro*, there is an optimum concentration for maximum penicillin activity and higher concentrations are actually less effective. A few hours elapse before the full bactericidal action of a dose of penicillin is achieved and the final process of bacterial lysis is accomplished by bacterial enzymes.

The action of penicillin is maximal at the pH of the body fluids and is little influenced by the presence of pus, blood and tissue autolysates. Moderate fever enhances its activity.

The injurious effects of penicillin on bacteria persist for some hours after the concentration of the antibiotic in the blood has fallen to barely detectable levels; for this reason penicillin therapy is often successful even when the scheme of dosage does not secure a continued bacteriostatic concentration of the drug. Cure of infection by penicillin is much less dependent upon the natural defence mechanisms of the body than is the case with sulphonamides, and the immunological responses to certain

organisms (for example  $\beta$ -hæmolytic streptococci) are much reduced in patients treated with penicillin. On the other hand in pneumococcal infections the production of antibodies is not prevented by penicillin.

**BACTERIAL RESISTANCE.** Many species of bacteria are resistant to the action of penicillin—natural resistance—but others may become resistant from contact with the antibiotic—acquired resistance. This phenomenon can readily be produced *in vitro* in the case of staphylococci and much less readily with streptococci and pneumococci. Organisms which have been rendered resistant in this way show altered morphological and staining characteristics, and their virulence is often reduced. Furthermore by repeated subculture in a penicillin-free medium they can be induced to regain susceptibility. On the other hand, organisms which become resistant *in vivo* show no morphological changes, they retain their virulence, and resistance—once fully developed—is permanent. They also produce penicillinase and so resemble naturally-resistant organisms which have never been in contact with penicillin. For further discussion of the mechanisms involved in bacterial resistance the reader is referred to the chapter on sulphonamides, p. 495.

In clinical practice the organism which shows the greatest tendency to develop penicillin resistance is *Staphylococcus aureus*; *Streptococcus viridans* also shows this characteristic but to a lesser degree. The former organism has become adapted to such a degree that the majority of strains isolated from patients in hospital are resistant to the drug. This does not apply to the community at large where most strains remain fully sensitive to penicillin. The development of penicillin resistance does not create resistance to other antibiotics, though staphylococci isolated from patients in hospital are often resistant to several antibiotics.  $\beta$ -Hæmolytic streptococci and pneumococci do not show this tendency to become resistant *in vivo*, but occasional resistant strains of gonococci and meningococci are encountered.

**PENICILLINASE.** Penicillinase is a bacterial enzyme which antagonises the action of penicillin. It is produced by non-sensitive bacteria and also by those strains of usually sensitive

## ANTIBACTERIAL AGENTS

organisms which are penicillin-resistant. On the other hand the fact that a particular organism produces penicillinase does not necessarily imply total resistance to the action of penicillin. Penicillinase hydrolyses penicillin to the inactive penicilloic acid.

In mixed bacterial infections—such as occur in wounds—the production of penicillinase by one species of organism may so inactivate penicillin that penicillin-sensitive organisms are unaffected, and complete failure of therapy results. Commercial preparations of penicillinase are used to test samples of penicillin for sterility, and the enzyme is also added to culture media to destroy penicillin and so facilitate the isolation of organisms from patients already under treatment with penicillin. Penicillinase has also been used successfully in the treatment of sensitivity reactions to penicillin.

### MODE OF ACTION OF PENICILLIN

The exact manner in which penicillin interferes with bacterial metabolism and so exerts a bactericidal action has not been explained, but a number of factual data are available as pointers in this direction. Penicillin reduces the ability of organisms to transfer glutamic acid from their environment to within the growing cell and thus interferes with protein synthesis. Sensitive organisms strongly bind penicillin whereas resistant organisms have less capacity to fix the drug to the bacterial cell. However, sensitive organisms during the resting phase also bind penicillin without being killed and a medium permitting active bacterial multiplication is also essential for the bactericidal action of penicillin to become apparent.

### ABSORPTION, FATE AND EXCRETION

*Absorption.* When penicillin is given by mouth only a small proportion of the dose is absorbed into the blood. The drug is partly destroyed by hydrochloric acid in the stomach, and in the small intestine penicillin which has not been inactivated is poorly absorbed. The remainder is inactivated by penicillinase produced by coliform organisms in the large bowel so that negligible amounts of active penicillin appear in the faeces. In infants, in whom hydrochloric acid secretion is low, less destruction occurs

and it is correspondingly easier to obtain adequate blood levels. In adults less than 20 per cent of the dose of benzylpenicillin is absorbed in biologically active form, but up to 40 per cent of phenoxymethylpenicillin may be absorbed. The latter preparation is usually preferred for oral administration on this account. Peak blood levels are attained in from 30–60 minutes after oral administration. Because of the poor absorption of penicillin from the gut, parenteral administration is essential in severe infections.

Benzylpenicillin is readily absorbed after subcutaneous or intramuscular injection and the latter route is the standard method of administration. Aqueous solutions are so rapidly absorbed that peak blood levels are reached in 15–30 minutes. When repository forms of penicillin are employed absorption is much delayed and may continue for days or even weeks if large doses are given. Penicillin is also absorbed from mucous and serous surfaces but these routes of administration are not employed except for local effects.

*Fate.* After absorption penicillin is widely distributed in the body, but very low concentrations are attained in serous cavities, the CSF and nervous tissue. The kidney contains high concentrations of the drug and intermediate amounts are found in muscle and other tissues. The plasma level is much higher than that of the tissues except the kidney. The fact that penicillin traverses the blood/CSF barrier poorly, even when the meninges are inflamed explains why intrathecal injections are often given in pyogenic meningitis to supplement systemic therapy. Reference is made in the section dealing with individual preparations to the peculiar distribution of penethamate hydriodide. Penicillin circulates in the blood partly bound to the plasma albumin, about 60 per cent of total drug in the case of benzylpenicillin. Very little is found within the red blood cells. Up to 50 per cent of penicillin in the body may be rendered biologically inactive, but the degradation mechanisms have not been defined.

*Excretion.* Penicillin is very rapidly excreted by the kidney—up to a total of some 90 per cent of the administered dose. About one-half of the drug absorbed is excreted in the first hour and this

## ANTIBACTERIAL AGENTS

accounts for the very rapid decline in plasma levels of penicillin, and consequent difficulty in maintaining continuing bactericidal concentrations by intermittent intramuscular injections of benzylpenicillin. Penicillin is excreted both by glomerular filtration and tubular excretion, and the renal clearance reaches a maximum of about 500 millilitres per minute which approximates to the effective renal plasma flow. In infants and patients with impaired renal function, excretion of penicillin is less rapid, and there is a corresponding persistence of effective plasma levels of the drug. A number of drugs are known which inhibit the tubular excretion of penicillin. Probenecid, which is described on p. 53, is employed to maintain high plasma levels of penicillin in the treatment of resistant *Streptococcus viridans* endocarditis. A small amount of penicillin is excreted in the bile, and concentrations of the drug in this fluid are higher than in the plasma. Negligible amounts leave the body in other secretions, for example in the sweat and tears.

## UNITAGE AND ASSAY

Penicillin dosage is expressed in units except in the case of phenoxymethylpenicillin in which the dose is given in milligrammes. The reason is that the older preparations of penicillin were impure, consisting of variable admixtures of naturally occurring penicillins with differing antibacterial activity. In order that the activity of different preparations might be stated the Unit was introduced in 1944 by international agreement. This was defined as the specific penicillin activity (measured by microbiological assay) of 0.6 microgram of pure sodium benzylpenicillin. Modern preparations of penicillin are virtually chemically pure and dosage could now be given in milligrams, but the unit system is still used: 1 mg. of pure benzylpenicillin sodium salt contains 1,667 units of activity. 1,000,000 units is called a Mega unit.

A variety of chemical, physical and microbiological methods are used to assay penicillin. In clinical practice the small amounts present in body fluids are measured by microbiological methods. The technical details are beyond the scope of this book.

## PREPARATIONS AND DOSES

A large number of preparations of penicillin are available. They fall into three main categories: (1) Benzylpenicillin given by intramuscular injection. (2) Various salts of benzylpenicillin given by intramuscular injection from which benzylpenicillin is released slowly, and prolonged blood levels are thereby maintained. (3) Preparations for oral administration. Attempts have also been made to produce penicillins less likely to result in sensitisation reactions, but these are not in general use; preparations of benzylpenicillin for topical application are also available commercially. The more important preparations are described below.

BENZYL-PENICILLIN is either the sodium or potassium salt, and is a white, crystalline powder freely soluble in water. It is dispensed for use in sterile sealed containers, the total amount of penicillin in Units being stated on the label. In this state it retains its activity for several years. Solutions for injection—Benzylpenicillin Injection—are prepared by dissolving the contents of the container in Sterile Water for Injection. The solution should be used within 14 days and stored at a temperature not exceeding 4° C. The total daily dose depends upon the type and severity of the infection under treatment and may vary from 0.5 Mega Unit to many Mega Units daily. Injections are usually given intramuscularly at 6- or 12-hourly intervals and the strength of solution used varies with the total amount to be given daily. Solutions containing more than 250,000 Units per ml. are often painful.

Benzylpenicillin is also available in tablets for oral use, the usual strength being 200,000 Units in each tablet. They should be kept in a well-closed container and stored in a cool, dry place. Oral administration of benzylpenicillin is suitable for infants and young children, but for adults phenoxymethylpenicillin is preferred. Oral benzylpenicillin should be given at 4-hourly intervals.

A variety of preparations of benzylpenicillin are available for topical use. These include eye-drops, ear-drops, creams, lozenges and dusting powders. Such preparations, however, are liable to cause sensitisation reactions and current practice favours the use of antibiotics less liable to produce allergic reactions when local

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medication is indicated. Preparations for local use are no longer included in the BP.

**PROCAINE PENICILLIN.** This preparation is the procaine salt of benzylpenicillin. It contains approximately 40 per cent of procaine and is a white powder soluble in 200 parts of water. It is dispensed in sealed containers with suitable bacteriostatic and buffering agents. Procaine Penicillin Injection is prepared by suspending the contents of the container in Sterile Water for Injection. The strength of the injection is 300,000 Units per ml. Benzylpenicillin is slowly released from the intramuscular injection site so that effective blood levels may be maintained for 12-48 hours following a single injection. The usual dose is 600,000 units to 1,200,000 Units daily. The BP also contains a "Fortified Procaine Penicillin Injection". This contains 300,000 Units of procaine penicillin and 100,000 units of benzylpenicillin per ml. of suspension. The addition of benzylpenicillin is designed to produce an initially higher concentration in the blood of penicillin than can be achieved by procaine penicillin alone. One to three ml. of the suspension is the usual range of dosage. Procaine penicillin suspended in arachis oil with 2 per cent aluminium monostearate (PAM) gives even greater delay in absorption after intramuscular injection and this preparation is widely used in the treatment of syphilis. Each ml. of suspension contains 300,000 Units of penicillin and the usual dose is 600,000 Units daily.

**BENZATHINE PENICILLIN** is another slow-release type of penicillin consisting of the *N-N*-dibenzylethylenediamine salt of di(benzylpenicillin). It is very insoluble in water. When given intramuscularly in aqueous suspension benzylpenicillin is slowly released and effective blood levels can be maintained for several days or weeks depending upon the dose. The usual strength of suspension employed is 300,000 Units per ml. The injections tend to be painful. Benzathine penicillin injections have been used in the treatment of syphilis and for the prophylaxis of rheumatic fever. Given orally it is less liable to destruction by hydrochloric acid in the stomach than is benzylpenicillin, but



effective plasma levels are not maintained for appreciably longer than with the latter preparation. It is available in tablets each containing 200,000 Units and the BP suggests a dose of 300,000-600,000 Units every 6 hours.

**BENETHAMINE PENICILLIN.** This non-official repository preparation of benzylpenicillin is the *N*-benzyl- $\beta$ -phenethylamine salt. It is given intramuscularly in aqueous suspension containing 300,000 Units per ml. In duration of action it falls between procaine penicillin and benzathine penicillin though the blood levels attained tend to be higher than with the latter preparation. The injections are painful.

**PHENOXYMETHYLPENICILLIN (Penicillin V).** This penicillin differs from benzylpenicillin in the side-chain attached to the  $\beta$ -lactam ring. Its absorption from the small intestine is better than that of benzylpenicillin and it is the preparation of choice for oral administration in adults. It is dispensed as tablets each containing 125 mg. which should be stored with the same precautions as those observed for benzylpenicillin. The usual dose is 125-250 mg. every 4 hours. 125 mg. is equivalent to 200,000 Units approximately. Phenoxyethylpenicillin is given by mouth only.

**OTHER PENICILLINS.** *Penethamate Hydriodide.* This ester of penicillin is diethylaminoethylbenzylpenicillin hydriodide. In animals and man it diffuses more readily into lung tissue and nervous tissue than does benzylpenicillin. Higher concentrations of penicillin have been found in the sputum after intramuscular injection of penethamate hydriodide than following the same dose of either procaine penicillin or benzylpenicillin. The ester itself is inactive, and its antibacterial activity is dependent upon the release of benzylpenicillin in the tissues. It has been proposed for use in pulmonary infections. There is, however, no conclusive evidence that the results of treatment with penethamate are superior to those obtained with benzylpenicillin. Furthermore it is more likely to produce allergic reactions and should be used with care. The dose by intramuscular injection is the same as for

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benzylpenicillin. *l*-Ephenamine Benzylpenicillin and allylmercaptomethylpenicillin (*Penicillin O*) have been used in patients who have become sensitised to benzylpenicillin, as they were thought less likely to elicit allergic responses. Neither preparation is, however, free from this propensity and they are not in general use.

### TOXIC EFFECTS

The lack of toxic effects from penicillin constitutes a major advantage with this drug. Enormous doses giving blood levels of 300 Units per ml. have been given to man on many consecutive days without toxic effects. Nevertheless the drug is not without danger and death has resulted from allergic reactions to penicillin.

REACTIONS AT INJECTION SITES. Aqueous injections are often painful, especially when concentrated solutions are used; and when oil is used as a vehicle local induration is not uncommon. Procaine penicillin and benzathine penicillin are relatively free from local reactions and because of a local anæsthetic effect are relatively painless. If penicillin is accidentally injected into a nerve trunk permanent destruction of nerve fibres may occur and it is essential that injections into the gluteal muscles should be given into the upper and outer quadrant well away from the sciatic nerve.

ALLERGIC REACTIONS. These are the most important untoward effects of penicillin therapy. Fortunately, the overall incidence is low, though it is increasing, and allergic reactions seem to occur more frequently in America than in this country. Reactions may be immediate, delayed, or of the "contact dermatitis" type. Immediate reactions take the form of acute anaphylactic shock and a number of fatalities have been reported. The clinical features are the same as those of anaphylactic shock following the injection of foreign protein and call for immediate treatment with full doses of adrenaline and the provision of an unobstructed airway.

The delayed type of reaction comes on 24 hours to 4 weeks after treatment has been started, but is most common between the 5th and 14th days. The clinical features closely resemble serum

sickness. The most frequently recognised manifestation is an urticarial skin eruption but almost any morphological type may occur including erythematous, morbilliform, multiform and rarely exfoliative. Pyrexia, arthralgia, lymphadenopathy, splenomegaly, angioneurotic œdema, asthma and rhinitis may also be seen, and in severe cases the clinical syndrome may be indistinguishable from polyarteritis nodosa. Minor reactions can be controlled with adrenaline and antihistaminics, but in severe reactions steroid therapy may be required. Penicillinase has also been used successfully in the treatment of this type of allergy.

Penicillin is a potent sensitising agent when used topically on skin or mucous membranes, producing an eczematous reaction which may later involve the whole skin surface. Although these local reactions usually clear up when the drug is withdrawn, patients so sensitized may develop very severe reactions if they are given penicillin parenterally at a later date. For these reasons, and because antibiotics equally effective locally and less liable to produce local reactions are now available, penicillin is used in this way much less often than formerly.

The majority of patients who develop allergic reactions have had penicillin in some form on a previous occasion and they are aware of the fact. When penicillin therapy is contemplated the patient should be questioned about past treatment with the drug and reactions to it. If there is a history of reaction due to sensitivity alternative treatment should be considered. In cases of doubt, skin or conjunctival tests may provide evidence of hypersensitivity, but these are not altogether reliable in denoting sensitisation. On rare occasions the small amount of penicillin used in the skin test has precipitated severe effects in sensitised patients. It should be remembered that procaine can also produce allergic reactions when procaine penicillin is used. Penethamate hydriodide is especially liable to induce reactions and phenoxymethylpenicillin is more powerful in this respect than is benzylpenicillin. Because of the increasing incidence of these reactions attempts have been made to produce penicillins with less tendency to cause these unwanted effects: such preparations are Penicillin O and *l*-Ephenamine penicillin but they are not wholly devoid of toxicity. Although sensitisation to penicillin, especially of the contact type,

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may be very long lasting it is not always so, and there are many cases on record where penicillin has been given without untoward effect to patients who had previously experienced a reaction to it.

*Nature of Penicillin Sensitivity.* This is not definitely known, but the most acceptable explanation is that penicillin or a degradation product of it acts as a haptene and becomes attached to tissue proteins thereby forming a complex with antigenic properties. This may stimulate the production of antibodies, and the subsequent administration of penicillin would form fresh antigen which would then react with antibodies to produce the lesions seen. If this explanation is correct the antibody should be demonstrable. Recent claims suggest that this may have been achieved.

**OTHER SIDE-EFFECTS.** Large doses of penicillin given intrathecally or applied to brain tissue have produced convulsions, meningeal irritation and radiculitis, but these untoward effects have been virtually eliminated by the use of pure benzylpenicillin and the avoidance of unnecessarily large doses of the drug. The Herxheimer reaction to penicillin employed in the treatment of syphilis is referred to on p. 541. Supra-infection with penicillin-insensitive organisms—notably Staphylococci and Monilia—may give pulmonary infection or enteritis, but the incidence is low. Mild diarrhoea is not uncommon when large doses of benzylpenicillin are given by mouth; the use of phenoxymethylpenicillin largely avoids this side-effect.

When penicillin is given orally or used as lozenges in mouth and throat infections a black, hairy tongue may result. The cause is not known with certainty. Various factors such as nicotinic acid deficiency, alteration of the normal oropharyngeal bacterial flora and a direct tendency of penicillin to increase cornification of mucosal epithelium may all play a part. It usually occurs after treatment for about a week and clears up, though slowly, sometimes even without interruption of penicillin therapy.

## THERAPEUTIC USES

The remarkable results of penicillin in the treatment of infections can hardly be overestimated and nearly twenty years after

its introduction it remains the single most important chemotherapeutic agent. For full details of therapy standard textbooks on therapeutics should be consulted and in this section the main indications only are presented.

**PNEUMOCOCCAL INFECTIONS.** Penicillin is the treatment of choice in all pneumococcal infections. All strains of this organism are sensitive to the drug. Uncomplicated pneumococcal pneumonia in young adults responds to as little as a single injection of 600,000 Units of procaine penicillin, but as a general rule therapy should be continued for 5-7 days. Phenoxymethylpenicillin is also effective in an oral dose of 125-250 mg. every 4 hours for a similar period. In elderly patients in whom pneumonia is often rapidly fatal, parenteral therapy is to be preferred. In patients with chronic bronchitis and acute exacerbations of pulmonary infection a mixed flora of pneumococci and *H. influenzae* are often found. In these cases high dosage with penicillin 0.5-1 Mega Unit every 6 hours combined with 1 G. of streptomycin twice daily may be life-saving.

Pneumococcal meningitis requires massive dosage up to 1 Mega unit of benzylpenicillin intramuscularly every 2 hours, combined with the intrathecal injection of 10,000-30,000 Units of benzylpenicillin daily. A sulphonamide is often given by mouth as well as penicillin. Therapy should be continued for 2-3 weeks, and surgical drainage of infected foci may be required. Pneumococcal endocarditis requires high dosage for at least 2 months, but relapse is not uncommon and repeated courses of treatment may be needed.

**STREPTOCOCCAL INFECTIONS.** In  $\beta$ -haemolytic streptococcal infections penicillin remains the treatment of choice, as bacterial resistance to a degree which renders penicillin ineffective does not occur. The multitudinous infections caused by this organism all respond to penicillin, though in meningitis and empyæma local instillation is essential in addition to parenteral therapy. When there is difficulty of access of the drug to the infecting organism, such as occurs in bacterial endocarditis, high dosage for prolonged periods may be needed. In the treatment of rheumatic fever or in

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acute glomerulonephritis, penicillin does not alter the immediate course of the disease. Nevertheless, living hæmolytic streptococci are often present in the throats of these patients, and there is now substantial evidence to show that continued low-grade rheumatic activity is accompanied by the presence of living organisms in the body. Furthermore, the evidence is incontrovertible that recurrences of rheumatic fever in susceptible patients, can be prevented by the daily administration of penicillin (or sulphonamide) by mouth. For these reasons penicillin should be given to patients with rheumatic fever or acute nephritis to eradicate hæmolytic streptococci and, in the case of rheumatic fever, prophylactic treatment should be continued with phenoxymethylpenicillin 125 mg. twice daily. A long-acting repository form of penicillin can also be used, for example benzathine penicillin 1 Mega Unit by intramuscular injection every fortnight. The prognosis in *subacute bacterial endocarditis*—most cases of which are due to *Streptococcus viridans*—has been revolutionised by penicillin treatment. For preference an accurate assessment of the sensitivity of the infecting organism to penicillin should be made and thereafter treatment given with doses designed to provide adequate tissue levels of the drug. Treatment must be prolonged for at least 2 months, and in cases with relatively resistant organisms prolonged treatment with as much as 40 Mega Units of penicillin daily combined with streptomycin may be needed.

GONOCOCCAL INFECTIONS are rapidly cured with penicillin. Uncomplicated acute gonococcal urethritis in the male can be cured with one injection of procaine penicillin, or a few doses by mouth of phenoxymethylpenicillin. Penicillin is also successful in preventing infection after exposure to possible infection if taken within 2 hours. Gonococcal infections elsewhere in the body, including arthritis and meningitis, respond well to penicillin given in large doses.

MENINGOCOCCAL INFECTION is susceptible to penicillin therapy, but sulphonamide therapy is the treatment of choice and combined therapy is often used (p.506 ).

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**STAPHYLOCOCCAL INFECTIONS.** Provided the infecting organism is sensitive to penicillin excellent results are obtained, but surgical drainage of residual abscesses is often required. In hospital practice many strains are now penicillin-resistant and other antibiotics, for example erythromycin or novobiocin, are required.

**ACTINOMYCOSIS.** Penicillin is the best agent in the control of this disease. Prolonged therapy is required and sulphonamide can often be added with advantage. Surgical drainage of abscesses is often needed. Anthrax also responds to penicillin and sulphonamide therapy.

**SYPHILIS.** Penicillin is the drug of choice in the treatment of this disease. Examples of schemes of dosage are mentioned in Chapter 16, with other drugs used in the treatment of syphilis.

**YAWS** is similarly highly amenable to treatment by means of penicillin.

Other infections which respond well to penicillin include Vincent's stomatitis, rat-bite fever and sensitive streptococcal urinary tract infections. Penicillin is also used in the treatment of diphtheria, gas-gangrene and tetanus to eradicate the infecting organisms. Reference has already been made to the fact that treatment with specific antitoxin is essential in these conditions to neutralise the powerful toxins which the organisms produce and which are responsible for the clinical manifestations of these infections.

## PROPHYLAXIS

The use of penicillin in the prevention of streptococcal infection in rheumatic subjects has already been mentioned, and it may also be used to control outbreaks of  $\beta$ -haemolytic streptococcal infection in residential schools and other institutions. Patients with congenital or rheumatic heart disease should have adequate penicillin cover prior to tooth extraction, tonsillectomy or similar surgical procedures. A single large dose—1 Mega Unit of benzylpenicillin—given intramuscularly half an hour before the procedure, followed by a similar dose 2 hours after the operation, is probably

## ANTIBACTERIAL AGENTS

adequate, and long-continued therapy both before and after the operation is undesirable.

Penicillin is extensively used to prevent infection after surgical operations and when potentially infected wounds are sustained. It is also used to prevent postoperative pulmonary infection and aspiration pneumonia in the comatose. Objection has been raised to this practice on the grounds that it favours the development of resistant strains and may render the patient allergic to the drug. Many physicians prefer to withhold penicillin until signs of infection appear. Penicillin is also used to prevent infection in drug-induced agranulocytosis until the white cell count has returned to normal.

## STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

Streptomycin is an antibiotic produced by the growth of the soil organism *Streptomyces griseus*: it was discovered in 1944 by Waksman. Dihydrostreptomycin, obtained from streptomycin, has similar properties and the two drugs will be described together. Their differences will be indicated in the text.

The chemistry of streptomycins is complex. They are organic bases with a glycosidic linkage and readily form salts with acids such as sulphuric acid. The salts are white crystalline powders, almost odourless and tasteless, freely soluble in water, but insoluble in the common organic solvents.

## ANTIBACTERIAL ACTIONS

Streptomycin is an antibiotic with a wide range of activity (especially against Gram—ve organisms) when tested *in vitro*, but because of the ready emergence of resistant strains it is used therapeutically in comparatively few infections. The most important organism susceptible to its action is *M. tuberculosis*. Indeed streptomycin was the first effective chemotherapeutic agent in tuberculosis. In infections due to the following organisms streptomycin is of therapeutic value and, in some, is the treatment of choice: *Pasteurella tularensis*, *P. pestis*, *Hæmophilus*



*influenzæ*, *Klebsiella pneumoniae*, *Brucella*, *Actinomyces*, and *H. ducreyi*.

*E. coli*, *Proteus vulgaris* and *Ps. pyocyanea* are also susceptible but readily become resistant. Gram-+ve cocci including staphylococci and *Streptococcus viridans* are also sensitive; and the use of the drug may sometimes be indicated in such infections. Streptomycin readily leads to the production of resistant strains both *in vitro* and *in vivo* and this may occur with great rapidity. For this reason, with this antibiotic more than any of the others, bacteriological testing for sensitivity is necessary. Streptomycin is bacteriostatic in low concentrations but bactericidal in higher concentrations which can readily be obtained with therapeutic doses in man.

*Mode of Action.* A variety of cellular biochemical mechanisms have been reported to be blocked by streptomycin, but no complete explanation of its action is yet available. Its activity is little influenced by the body fluids, pus or necrotic tissue, but *in vitro* the optimum pH is around 8 and in more acid media some diminution in activity results.

**DRUG RESISTANCE.** Organisms including *M. tuberculosis* readily become resistant to the drug and this is one of the serious drawbacks to its use. Fortunately, in the treatment of tuberculosis combination with isoniazid or with sodium aminosalicylate prevents the occurrence of resistance, and streptomycin is never used alone in tuberculosis. It is believed that resistance is due to the presence of naturally resistant strains in the bacterial inoculum and these flourish as the sensitive strains are killed by streptomycin. It is also possible to produce *in vivo* and *in vitro* strains of organisms which are actually dependent on streptomycin for their continued growth. Cross-resistance with other antibiotics is not conferred by streptomycin but organisms rendered resistant to streptomycin are also resistant to dihydrostreptomycin. The mechanism of development of resistance is not known but there is no evidence that streptomycin-resistant organisms produce substances which destroy streptomycin (see penicillinase, p. 436).

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### PREPARATIONS, ADMINISTRATION AND DOSAGE

Streptomycin is prepared for use as Streptomycin Sulphate. Other salts, for example a calcium chloride complex, are also available but they possess no advantage over the sulphate. Streptomycin sulphate is dispensed in sealed ampoules, and it retains its potency for at least two years. The salt is freely soluble in water and is administered by intramuscular injection. The daily dose is 0.5–1 G. but larger doses are sometimes given. Before use the salt is dissolved in Sterile Water for Injection, a concentration of 1 G. in 3 ml. being suitable. Twice-daily injections are commonly employed in non-tuberculous infection, but in tuberculosis the drug is not given more often than once a day. Solutions for injection retain their activity for several days at room temperature, and they may be kept at temperatures below 20° C. for many months. Multiple-dose vials of Streptomycin Sulphate Injection are available commercially. Streptomycin sulphate is also used intrathecally in a dose of 25–100 mg. depending upon the age of the patient. The dose is dissolved in 2.5–10 ml. of Sodium Chloride Injection before use.

Dihydrostreptomycin Sulphate is given intramuscularly in the same dose as streptomycin sulphate. The usual strength of solution employed is 1 G. in 4 ml. This solution is less stable than Streptomycin Injection and should be used within one month of preparation when stored in a refrigerator. *The dihydro derivative must not be injected intrathecally.*

Streptoduocin (BP Commission Approved Name) is a mixture of equal parts of streptomycin sulphate and dihydrostreptomycin sulphate. It is given intramuscularly in the same total dosage as its component salts but it is not employed intrathecally. Other routes of administration of streptomycins, for example by aerosol in pulmonary infections and orally as intestinal chemotherapeutic agents, are not recommended.

### ABSORPTION, FATE AND EXCRETION

Streptomycin is not absorbed into the blood when given by mouth but it is not destroyed in the gastro-intestinal tract. It acts

as an intestinal bactericidal agent, but because of the rapid emergence of resistant organisms it is not the antibiotic of choice for this purpose. After intramuscular injection streptomycin is quickly absorbed and peak blood levels are reached in 1-1½ hours. With the customary dose of 0.5-1 G. the blood concentration reaches 20-40 µg. per ml. and falls rather rapidly over a period of 6-8 hours. Effective therapeutic levels can be maintained for this time. Streptomycin is distributed mainly in the extracellular fluids and it does not readily penetrate into the serous cavities of the body unless the membranes are inflamed. Hence the levels in the CSF are negligible unless meningitis is present (the pathological meninges fail to act as a barrier), and in this condition intrathecal administration is often needed. Streptomycin is excreted by the kidney and some 70 per cent of the dose may be recovered in active form in the urine. The fate in the body of the remainder is unknown. Excretion is accomplished by glomerular filtration only and in patients with impaired renal function great care is needed, as prolonged high blood levels of the drug may then occur. Serious ototoxicity may supervene in such patients even after a few days administration. A small amount of streptomycin is excreted in the bile.

### TOXIC EFFECTS

Streptomycin evokes a number of toxic reactions of which neurotoxicity involving the 8th cranial nerve is the most serious. Hypersensitivity reactions are also not uncommon.

**HYPERSENSITIVITY.** The commonest effect is a skin eruption and in severe cases drug fever, lymphadenopathy, joint pains and eosinophilia may also be present. The usual drug eruption is maculopapular or urticarial with pruritus, but rarely in severe cases exfoliation may occur. These effects usually appear during the first few weeks of treatment. In mild cases antihistaminics may give relief and the reaction may subside to allow therapy to be continued. In severe cases the drug should be withdrawn and if continued therapy is essential—as for example in tuberculosis—desensitisation with gradually increasing daily doses should be carried out. Skin sensitivity often occurs in persons who regularly

## ANTIBACTERIAL AGENTS

handle streptomycin solutions, e.g. nurses and pharmacists. They should wear protective rubber gloves when handling such solutions. Very rarely streptomycin has caused bone-marrow depression and a few deaths from aplastic anæmia have been attributed to the drug.

**OTOTOXICITY.** Damage to the vestibular and cochlear divisions of the 8th cranial nerve is the most serious toxic effect of streptomycin. The parent substance is more likely to cause vestibular disturbance while dihydrostreptomycin produces a greater incidence of deafness. These effects are due to direct toxic damage to nervous tissue, though some doubt exists as to whether the central nuclei or the peripheral labyrinthine end-organs are primarily damaged by the drug. The results, however, are loss of balance with ataxia, especially in the dark, and difficulty in walking on soft and uneven surfaces. The onset of labyrinthine disturbance is often heralded by headache, but nausea, vomiting and acute vertigo may supervene. This condition is more likely to occur in the elderly patient than in the young, and is a function of the duration of therapy and dosage. High blood levels of streptomycin maintained for a short time may cause labyrinthine damage, while lower levels for a longer time may prove equally toxic. Younger subjects may learn to compensate for the disability quickly but recovery is slow and residual damage frequent. Elderly patients with impaired renal function are especially liable to develop this toxic effect, and streptomycin should be employed with great caution in these patients. Intrathecal injection is more liable to cause vestibular damage than intramuscular injection, and more than 100 mg. of streptomycin should never be injected as a single dose by this route. Deafness is also caused by streptomycin, especially if it is given intrathecally. Tinnitus heralds its onset, and if the drug is then stopped serious loss of hearing is prevented. It is not often a problem with the lower dosage now employed except in elderly subjects with poor renal function. Prevention lies in using the smallest dose compatible with efficient treatment and streptomycin should only be employed when other chemotherapeutic agents are likely to prove ineffective.

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*Dihydrostreptomycin* causes loss of hearing more readily than loss of vestibular function. Because deafness is the more serious disability this preparation should only be used after deliberate consideration and it must never be given intrathecally.

*Streptoduocin* was introduced to diminish the incidence of 8th nerve damage. The danger is less because of the smaller dosage of each component; but the total dose ensures that there is no loss of therapeutic efficiency. Deafness has, however, occurred after its use and the general consensus of opinion is that dihydrostreptomycin should be avoided at least for long-term therapy.

MISCELLANEOUS TOXIC EFFECTS. Local irritation at the site of injection may be caused by streptomycin and repeated injections into the same area should be avoided. Reference has already been made to the enhanced tendency to ototoxicity after intrathecal injection of streptomycin; occasionally, especially when unnecessarily large doses have been employed, acute neuropathy—with severe root pain and paraplegia—has followed its use by this route.

Nausea and vomiting are uncommon and these symptoms can usually be controlled by anti-emetic drugs. The earlier preparations of streptomycin sometimes produced renal tubular damage but the modern preparations have eliminated this toxic property. Similarly, acute allergic reactions with hypotension, bronchospasm and marked cutaneous vasodilatation are now very rare.

### THERAPEUTIC USES

By far the most important use of streptomycin is in the treatment of tuberculosis and this aspect is discussed on p. 487. Streptomycin is the antibiotic of choice in Tularæmia and in Plague. In the former infection 1 G. given daily for 5–7 days is usually adequate, and in Plague a daily dose of 2 G. until the temperature has fallen to normal levels followed by 1 G. daily for a further 5–7 days is recommended. Concomitant therapy with a systemic sulphonamide in full doses is often employed in the treatment of Plague.

In meningitis due to *H. influenza*, streptomycin is the initial

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drug of choice both parenterally and intrathecally. Full doses should be employed and sulphonamide therapy instituted simultaneously. As relapse often occurs, sensitivity tests must be performed upon the organisms isolated from the CSF and other antibiotics used if streptomycin resistance develops.

In pneumonia due to *H. influenzae* and *K. pneumoniae* streptomycin may be valuable but sensitivity tests upon the organisms isolated from the sputum must be done to guide the physician in the choice of the most suitable antibiotic. A combination of penicillin and streptomycin is often the most effective therapy in patients with chronic bronchitis during acute exacerbations, and this type of therapy may also be required in subacute bacterial endocarditis which has failed to respond to penicillin alone.

In chronic brucellosis streptomycin with sulphonamide and a tetracycline may be required before the infection is finally eradicated.

In certain cases of Gram—ve infection of the urinary tract, streptomycin is of value. It is not, however, the first choice in the treatment of such infection, and it is only used when a satisfactory response to other remedies has not occurred and sensitivity tests indicate that it is likely to be successful (p. 449). A number of other infections, including chancroid and actinomycosis, are susceptible to streptomycin but as other chemotherapeutic agents are equally effective streptomycin is seldom used in these infections.

Although streptomycin has been employed locally in the treatment of skin infections, gastro-intestinal infection and pulmonary infection (by inhalation) its use in this way is not recommended as resistant variants quickly develop.

## THE TETRACYCLINES

Antibiotics of this group were discovered as a result of planned research by the American pharmaceutical industry. The project was designed to study soil micro-organisms which might produce potentially useful chemotherapeutic substances. Many thousands of soil samples were examined and as a result Chlortetracycline ("Aureomycin") was isolated in 1948 from a strain of streptomycetes

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named aureofaciens because of the golden colour of the antibiotic. In 1950 Oxytetracycline ("Terramycin") was obtained from *Streptomyces rimosus* and in 1952 Tetracycline itself was prepared from chlortetracycline, after the chemical structure of the tetracyclines had been determined. Tetracycline has also been obtained from an unnamed strain of streptomyces. Commercially, chlortetracycline and oxytetracycline are now obtained by deep-tank fermentation and tetracycline is manufactured by reduction of either substance.

### CHEMISTRY

The tetracyclines are described chemically as polycyclic naphthacene carboxamides and they differ from each other only in the possession of a Cl group (chlortetracycline) or OH group (oxytetracycline), which are absent in the case of tetracycline. The bases are amphoteric, yellow, bitter-tasting powders, sparingly soluble in water at pH 7 and forming both basic and acid salts. The latter are usually employed in therapeutics as they are stable in the dry powdered state. Assay is carried out microbiologically with reference to a standard preparation accepted internationally.

As might be expected from their close chemical relationships the pharmacological actions of the tetracyclines are very similar. They will be discussed together and notable differences will be indicated in the text.

### ANTIBACTERIAL ACTIONS

The tetracyclines are called "broad spectrum" antibiotics to indicate that they are effective against many different species of micro-organisms. Their range of activity includes an inhibitory or a destructive effect on rickettsiæ, large viruses of the lymphogranuloma-psittacosis group, Gram-+ve and Gram-—ve cocci and bacilli. *Leptospira*, *treponema*, *Mycobacterium tuberculosis*, and *Entamoeba histolytica* are also sufficiently susceptible to make the tetracyclines of limited value in infections with these organisms. *Proteus* and *pseudomonas* are generally resistant and small viruses are completely unaffected. Although differing degrees of susceptibility to the three members of the tetracycline group of anti-

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biotics can sometimes be demonstrated *in vitro* these are seldom of importance from the practical standpoint.

Tetracyclines act best against rapidly multiplying organisms and the action is bacteriostatic rather than bactericidal in the concentrations ordinarily attained in the body fluids. However, bactericidal concentrations may be attained in the urine and also in the bowel because of the limited absorption of these drugs given by mouth. Blood, serum and tissue autolysates do not appear to interfere with the antibiotic action and the immunological responses of the host are unaffected.

Resistance to the action of the tetracyclines develops slowly, and organisms rendered refractory to one member of the group are also resistant to the action of the other two congeners. Cross-resistance with chloramphenicol has been noted in the case of Gram-—ve bacilli but not with Gram-+ve cocci. By far the most important organism which has become resistant to these drugs is *Staphylococcus aureus*. This is the common finding in hospital practice and it is not rare for severe tetracycline-resistant staphylococcal supra-infection to supervene during treatment with these antibiotics (p. 460).

The mode of action of the tetracyclines is unknown. They interfere with protein synthesis by micro-organisms but the enzyme systems involved have not been defined. Resistant organisms have not been shown to produce antagonistic substances.

### ABSORPTION, FATE AND EXCRETION

*By Mouth.* Tetracyclines are only partly absorbed from the gastro-intestinal tract, but they are not destroyed by gastric juice nor by micro-organisms in the colon. It appears that they combine readily with multivalent metallic ions such as calcium and aluminium and the resulting complex is poorly absorbed. This explains why aluminium hydroxide (given in an attempt to avoid gastric upset) leads to poor absorption and calcium diphosphate used as a "filler" in capsules similarly hinders absorption. On the other hand citric acid or sodium metaphosphate enhances absorption by binding calcium in the intestine and so rendering the ion unavailable to combine with tetracycline. Food per se does not



significantly interfere with absorption. Of the three congeners tetracycline is absorbed more quickly and more completely than the other two. Peak plasma levels after a single dose are reached in 2-4 hours and are maintained for 6-8 hours. Average plasma levels with the usual therapeutic doses reach 1-5 micrograms or more per ml., and doubling the dose does not lead to a corresponding rise in the plasma level. The fraction of the dose not absorbed remains biologically active in the bowel and leads to marked suppression of the normal flora with overgrowth of resistant organisms. The stool tends to become soft, yellowish-green in colour, and relatively odourless. Given *intramuscularly* chlortetracycline is irregularly absorbed and it is not administered by this route. Oxytetracycline and tetracycline are satisfactorily absorbed and adequate levels may be maintained with 6- or 12-hourly dosage. The injections are painful.

The tetracyclines are widely distributed in the body, attaining highest concentrations in the kidney, liver, spleen and lung. They diffuse poorly into the CSF and of the three, tetracycline reaches the highest concentrations in this fluid. When the meninges are inflamed diffusion is enhanced. Degradation of tetracyclines to inactive products occurs but the metabolic pathways are not known.

These drugs are excreted in the urine slowly, but up to 35 per cent of the ingested dose may eventually be recovered from the urine in active form. Larger amounts of tetracycline are excreted by this route than of chlortetracycline (5-10 per cent). A proportion of the drug is also excreted in the bile especially in the case of chlortetracycline, and concentrations 15 times as high as in the plasma may be found in this fluid. It follows that in urinary tract infections and in meningitis tetracycline is the most appropriate drug if a tetracycline is indicated; in biliary tract infections chlortetracycline may be preferred.

#### PREPARATIONS, ADMINISTRATION AND DOSES

For systemic effects the tetracyclines are usually given by mouth, but they may also be administered by intravenous and intramuscular injection; many preparations are also available for topical use.

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*Oral Preparations* of all three tetracyclines are official in the BP 1958. Chlortetracycline Hydrochloride is dispensed in capsules each containing 250 mg. The drug is given at 6-hourly intervals and the BP suggests a total daily dose of 1-3 G. for an adult; for a child 10-30 mg. per Kg. of body weight is the usual daily dose, and capsules containing 50 mg. of the drug may be dispensed for pædiatric use. Oxytetracycline is given orally as the dihydrate. The dosage is the same as for chlortetracycline. Tetracycline Hydrochloride is given in the same doses and both capsules and sugar-coated tablets are official preparations.

To facilitate administration to children a variety of flavoured suspensions is available commercially. A further modification, the rationale of which has been discussed, is the use of tetracycline hydrochloride with sodium hexametaphosphate to facilitate absorption, and capsules containing 250 mg. of tetracycline with 380 mg. of sodium metaphosphate are available.

*Preparations for Parenteral Use.* Chlortetracycline, oxytetracycline and tetracycline may be given intravenously when oral administration is impossible or when the severity of the illness suggests initial intravenous medication. The hydrochloride is used and a freshly prepared solution is given by intravenous infusion in a concentration not exceeding 0.1 per cent w/v. Stronger solutions are apt to cause venous thrombosis. The solution is buffered with sodium glycinate. The usual adult dose is 0.25-0.5 G. at 6- or 12-hourly intervals and for a child 10-20 mg. per Kg. of body weight daily.

Oxytetracycline and tetracycline hydrochloride may also be given by intramuscular injection, and the BP lists an injection with procaine for each drug to be given by this route only. The usual daily dose for an adult is 0.2-0.4 G. in divided doses at 6-, 8- or 12-hourly intervals. For a child 5 mg. per Kg. of body weight is usually given daily. These injections are painful—hence the addition of procaine—and solutions stronger than 5 per cent w/v, for example 100 mg. in 2 ml., should not be used. Chlortetracycline is not given intramuscularly because absorption is very irregular by this route. Many preparations of the tetracyclines are used locally including eye ointments and eye-drops, ear-drops,

ointments for application to the skin, lozenges, and powders for application to wounds. The strengths employed vary from 0.5 per cent in the case of ophthalmic preparations to 3 per cent for skin preparations. These preparations are non-official but are available as proprietary preparations.

### TOXIC EFFECTS

The common side-effects of the tetracyclines involve the gastro-intestinal tract and include anorexia, nausea, vomiting and epigastric discomfort. These effects are apparently due to a local irritant action of the drug and may be partly avoided by giving the antibiotic with or after food. The use of antacids containing calcium or aluminium is to be avoided as these ions hinder absorption of tetracyclines. The incidence of gastric disturbance is greatest when oxytetracycline is used and least with tetracycline.

Mucosal changes including stomatitis, glossitis, black tongue, irritation in the anal region, and in women vaginal and vulvar irritation have often been described. Their exact cause is not known, but suppression of the normal mucosal bacterial flora with overgrowth of tetracycline-resistant organisms may be a factor. Some of the changes resemble those seen in Vitamin B deficiency and because of this some physicians advocate that Vitamin B supplements should be given when tetracyclines are administered for prolonged periods. The occurrence of all those side-effects bears some relation to the dose of tetracycline employed, as they are seen more often with large doses and prolonged treatment than with smaller dosage. They are uncommon with the usual therapeutic doses given for less than one week. The most serious effect of tetracycline therapy is the development of supra-infection with tetracycline-resistant *Staphylococcus aureus*. This is more likely to happen in hospital than in the patient's home. The usual manifestation is enterocolitis with profuse watery diarrhoea, but pulmonary infection and a syndrome with sore throat, fever and a scarlatiniform rash—staphylococcal scarlet fever—have also occurred. When tetracyclines are used in hospital practice careful observation of the patient is called for; should clinical features suggestive of staphylococcal infection arise, the drug should be stopped at once and the appropriate antibiotic—usually erythro-

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mycin—should be substituted. This may prove life-saving as the onset of staphylococcal enteritis in an already ill patient is an extremely grave complication. Appropriate supportive therapy to combat water and electrolyte depletion may also be needed. It should be noted that soft bowel motions with an increase in the number of stools per day often occur during oral treatment with tetracyclines, a finding which does not signify serious intestinal supra-infection. Less often infection with monilia may occur during the course of treatment with the tetracyclines. Allergic reactions are said to be less frequent than with penicillin or sulphonamides but they do occur and have the usual features of drug allergy. The most frequently observed signs are skin eruptions involving the interdigital and peri-orbital regions often with local œdema, and drug fever. Reference has already been made to the irritation produced by intramuscular injections of tetracyclines and to the venous thrombosis which may follow intravenous infusion of these antibiotics. In animals given large doses of tetracyclines intravenously, hepatic damage has been noted and this has also been reported in man. The doses employed in therapeutics do not cause this effect. The tetracyclines have not been implicated as a cause of bone marrow depression.

## THERAPEUTIC USES

Despite their wide range of activity there are comparatively few infections for which the tetracyclines provide essential therapy. They are mainly valuable when the patient has failed to respond to other antibiotics or sulphonamides because of the presence of resistant strains of normally sensitive organisms. They are also used when penicillin or sulphonamides cannot be given because the patient is allergic to these drugs. When mixed infection is present the tetracyclines may be the most appropriate remedy. Ideally, accurate bacteriological diagnosis should be available before tetracyclines are used, but in practice this is not always possible. They should not be used in trivial infections or as drugs of convenience in febrile conditions when bacteriological diagnosis is lacking. The rising incidence of tetracycline-resistant staphylococcal infection in hospital practice and its serious con-

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sequences is a further reminder of the potential dangers of indiscriminate use of these antibiotics.

### INFECTIONS IN WHICH TETRACYCLINES OFFER THE BEST TREATMENT

In rickettsial diseases—of which only “Q” fever is likely to be encountered in this country—tetracyclines are the treatment of choice. In those parts of the world where the various forms of typhus fever are common tetracyclines have completely altered the outlook. Full doses given by mouth for 10 days are usually curative.

PSITTACOSIS is best treated for one week with a tetracycline in the usual oral dose. In *lymphogranuloma venereum* tetracyclines are also the treatment of choice but in this condition prolonged therapy for several weeks may be needed in chronic relapsing cases.

ACUTE BRUCELLOSIS responds well to a tetracycline given for 2-3 weeks, but in the chronic form of the disease treatment is less satisfactory and combined therapy with streptomycin and sulphonamides - prolonged and repeated—may be needed before final cure results.

In GRANULOMA INGUINALE a tetracycline in conventional dosage should be given until the lesions heal, and *tularæmia* responds as well to these drugs as to streptomycin. Many physicians would also include infections with *Shigella sonnei* as a positive indication for tetracycline therapy, because such a high percentage of strains are now resistant to sulphonamides. Oxy-tetracycline is regarded as the antibiotic of choice and treatment for 6 days brings about bacteriological cure in over 95 per cent of patients with this infection.

### INFECTIONS FOR WHICH TETRACYCLINES ARE OF VALUE

PULMONARY INFECTIONS. Tetracyclines are often useful in patients with pulmonary infection who fail to respond to penicillin therapy. *H. influenzae*, Friedländer's bacillus and some

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strains of *Staphylococcus aureus* which are the common infecting organisms in penicillin-resistant pulmonary infection, are sensitive to tetracycline. It seems likely too that as yet unidentified viruses may be responsible for some pneumonias amenable to tetracycline therapy. The usual doses are employed. Tetracyclines have also been used prophylactically in patients with chronic bronchitis to prevent pulmonary infection, especially during the winter months. The smallest dose which will keep the sputum mucoid (that is to say, free from pus) is used—often 0.5 G. daily suffices—and some patients undoubtedly benefit from this type of therapy. A similar regimen is used in infants with mucoviscidosis. Whooping cough is also benefited by tetracycline treatment, especially if given early in the course of the disease.

URINARY TRACT INFECTIONS are often treated with tetracycline, when they have proved resistant to sulphonamide therapy. Infections due to *E. coli*, *A. aerogenes* and *Streptococcus faecalis* are likely to respond to treatment but infections with proteus and pseudomonas are resistant. The reaction of the urine should be kept acid, as tetracyclines are inactivated in an alkaline medium.

Infections elsewhere due to *E. coli*, for example peritonitis, are also frequently responsive to tetracyclines.

## MISCELLANEOUS USES

Tetracyclines have been used with success in the treatment of *H. influenzae* meningitis resistant to streptomycin therapy. Intravenous administration should be given as this offers the best prospect of securing an adequate level in the CSF.

They are also of value in the treatment of amœbiasis as adjuvant therapy (p. 566).

In SYPHILIS they have been used successfully in patients sensitive to penicillin: 5 G. daily by mouth for 10 days is the recommended dose.

In TUBERCULOSIS oxytetracycline is used in a daily dose of 2.5–5 G. usually with viomycin when the infecting organisms are resistant to the standard remedies.

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Claims have also been made for their efficiency in the treatment of threadworm infestation. Finally the tetracyclines are used locally in the eye, the ear, upon the skin, and in wounds when the infecting organisms are sensitive to their action. It should be remembered, however, that they can produce sensitisation when used in this way.

## THE ERYTHROMYCIN GROUP

Erythromycin is an antibiotic discovered in 1952 and produced by *Streptomyces erythreus*. It is obtained as a white, crystalline, bitter substance, sparingly soluble in water but soluble in alcohol. Its chemical structure has recently been defined.

### ANTIBACTERIAL SPECTRUM

Erythromycin is active against Gram-positive cocci including streptococci, staphylococci and pneumococci. *Neisseria*, *hæmophilus*, diphtheria bacilli, certain rickettsias and large viruses are also sensitive to the drug. Coliform bacilli, salmonellæ and shigellæ are insensitive. Erythromycin therefore resembles penicillin in its range of activity. Naturally occurring resistant strains are relatively uncommon but resistance can readily be produced *in vitro* and as a result of treatment with the drug. Cross-resistance occurs between erythromycin and carbomycin and to a lesser extent with spiramycin and oleandomycin. The drug may be bactericidal or bacteriostatic depending upon the concentration of the antibiotic present and the sensitivity of the organism. Its mode of action is not known but it appears to act best against rapidly multiplying organisms.

### ABSORPTION, FATE AND EXCRETION

Erythromycin is readily absorbed from the upper intestinal tract after oral administration. It is partly destroyed by the acid gastric juice and is administered as enteric-coated tablets. Peak blood levels are obtained 2-4 hours after ingestion and decline fairly rapidly by 6-8 hours. With doses of 250-500 mg. at 6-hourly intervals satisfactory blood levels can be maintained. Diffusion into the cerebrospinal fluid is low, but substantial amounts of

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active drug appear in the bile and some is present in the fæces. Concentration of the drug occurs in the tissues, for example the kidney and spleen. Only small amounts of active drug appear in the urine but satisfactory chemotherapeutic concentrations can be attained. The metabolic fate of the bulk of the drug is unknown.

### PREPARATIONS AND DOSES

Erythromycin Tablets are official in the BP 1958 and are commercially available in strengths of 250, 200 and 100 mg. They are enteric-coated. The usual daily dose is 1-2 G. given in divided doses every 4-6 hours. Preparations for intravenous use by slow intravenous infusion in saline or dextrose solutions are also available.

### TOXIC EFFECTS

Serious toxic effects from erythromycin are uncommon. Nausea, vomiting, abdominal pain and diarrhoea may occur, especially with large oral doses, but the intestinal flora is not suppressed to the same extent as with the tetracyclines or streptomycin. Allergic reactions are rare and bone marrow depression has not been reported. Occasionally moniliasis may occur, especially if treatment is prolonged.

### THERAPEUTIC USES

The main use of erythromycin is in the treatment of staphylococcal infection resistant to penicillin and other antibiotics. In such infections, which are now common, especially in hospital practice, the drug may be life-saving. Systemic infections which are susceptible to other remedies should not be treated with erythromycin as resistant strains can readily be produced. For the same reason topical application of erythromycin in skin infections is best avoided.

### CARBOMYCIN

This antibiotic which is produced by *Streptomyces halstedii* has a range of action almost identical with erythromycin, but it is therapeutically inferior. Cross-resistance with erythromycin is



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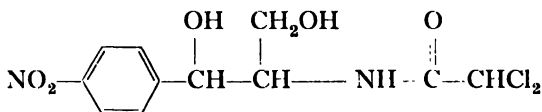
virtually complete. It cannot therefore be recommended for clinical use.

### SPIRAMYCIN AND OLEANDOMYCIN

These two antibiotics, which are produced by *Streptomyces ambofaciens* and *Streptomyces antibioticus* respectively, are also similar to erythromycin in their antibacterial spectra and pharmacological characteristics. Both antibiotics are generally considered to be less active than erythromycin *in vivo* but staphylococci which are resistant to erythromycin are not necessarily resistant to oleandomycin or spiramycin. These drugs have not yet been subjected to adequate clinical evaluation but it seems unlikely that they will have an important place in therapeutics.

### CHLORAMPHENICOL

Chloramphenicol is a wide-spectrum antibiotic originally obtained in 1947 from the culture medium of *Streptomyces venezuelæ*. It is now made synthetically. Its chemical structure is relatively simple:



It is a whitish, very bitter crystalline powder, sparingly soluble in water but soluble in organic solvents. It is stable over a wide pH range and resists boiling.

### ANTIBACTERIAL SPECTRUM

This is similar to that of the tetracyclines and includes a wide selection of Gram-—ve organisms, Gram-+ve cocci, rickettsiæ and the larger viruses of the psittacosis-lymphogranuloma group. The most important action of chloramphenicol is in the typhoid group of fevers where it is the only effective antibiotic. The drug has a bacteriostatic rather than bactericidal action and while

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resistance to its action may develop slowly, this does not represent a serious clinical problem. A number of effects on bacterial enzyme systems have been demonstrated but as yet no definite explanation of its mode of action is available.

### ABSORPTION, FATE AND EXCRETION

Chloramphenicol is readily absorbed from the gut after oral administration and maximum blood levels are reached about 2 hours later. This level falls to about half of the maximum in 6 hours and the drug has disappeared from the blood in 12-18 hours, depending upon the dose administered. Satisfactory blood levels can be maintained with a 6-hourly oral dosage schedule. Chloramphenicol circulates partly bound to the plasma proteins and it penetrates into the body fluids including CSF, where concentrations of about half those occurring in the blood are found. It is degraded in the liver and excreted by the kidney. Up to 90 per cent of the administered dose can be recovered from the urine: about 10 per cent is unchanged and the remainder consists partly of a hydrolysis product and partly of a glycuronic acid conjugate. In the tissues only the unchanged drug is biologically active, but adequate chemotherapeutic concentrations can be obtained in the urine.

### TOXIC EFFECTS

Bone marrow depression is the most important toxic effect of chloramphenicol: the white cell series, red cells and platelets may all be involved. A considerable number of fatal cases of aplastic anaemia have been attributed to chloramphenicol therapy and on this account the drug is now used more circumspectly. The true incidence of this serious complication is difficult to determine and it is undoubtedly rare, having regard to the total number of patients treated. Most of the deaths have followed prolonged treatment or repeated courses of treatment, but fatalities have also been reported after relatively small doses of this drug. In general, however, it is widely accepted that the greater the total dosage, the more likely it is that aplastic anaemia will occur. There is no special age or sex predilection. It is thought that the paranitrophenol component of the chloramphenicol

molecule is responsible for the depressant action on the bone marrow.

Other side-effects include gastro-intestinal disturbances which have been described in detail in the section on the tetracyclines, but these are less troublesome with chloramphenicol. Nevertheless supra-infection with organisms not susceptible to the drug may occur, for example moniliasis, and occasionally this may cause infection such as pneumonia.

Allergic manifestations including drug fever, joint pains, asthma and skin eruptions may also be seen, and skin sensitisation may follow local application of the drug. Optic neuritis and acute hæmolytic anæmia have been reported but they are extremely rare.

#### PREPARATIONS AND DOSES

For its systemic effects, chloramphenicol is usually given by mouth in Capsules containing 250 mg. in each. This is the only preparation included in the BP 1958. The total daily dose for adults is 1.5-3 G. given in divided doses every 6 hours. For children 50-75 mg. per Kg. of body weight is used as the total daily dose. Other preparations available for systemic administration include a suspension of chloramphenicol palmitate; each 4 ml. contain the equivalent of 125 mg. of chloramphenicol base and this preparation is convenient for pædiatric use. The drug may also be given by deep intramuscular injection when a 40 per cent aqueous suspension is employed, 1-1.5 G. being injected every 12 hours. For intravenous use a preparation containing 250 mg. per ml. dissolved in 50 per cent dimethylacetamide is available. This is best given by slow intravenous infusion in physiological saline or 5 per cent dextrose solution.

A 1 per cent ointment or 0.5 per cent borate-buffered eye-drops are used in infections of the eye, and a 5 per cent to 10 per cent solution in propylene glycol is used as ear-drops. Chloramphenicol cream, 1 per cent, is available for use in skin infections.

#### THERAPEUTIC USES

Chloramphenicol is the drug of choice in the treatment of the typhoid-paratyphoid group of fevers and these infections are the

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only absolute indication for its use. Full doses should be employed initially, 3-4 G. daily for an adult and 75 mg. per Kg. body weight for a child. Treatment should be continued for 10 days after the temperature has fallen to normal, as with shorter courses of treatment there is a greater tendency for relapse to occur. Although many other infections can be treated satisfactorily with chloramphenicol it is wise to restrict its use to infections which endanger life and are resistant to other remedies. Applied locally, chloramphenicol is used in the treatment of susceptible infections of the conjunctiva. In chronic otorrhœa it is particularly effective when *Proteus vulgaris* or *Ps. pyocyanea* are the infecting organisms. It is also used in pyogenic skin infections.

## NEOMYCIN

This antibiotic, discovered in 1949 by Waksman and Lechevalier, is produced by the growth of a selected strain of *Streptomyces fradiae*. It is a yellowish-white, hygroscopic powder, freely soluble in water and stable in the dry state and in solution. Its chemical constitution has not been determined.

### ANTIBACTERIAL PROPERTIES

Neomycin has a wider range of antibacterial activity than penicillin or streptomycin including both Gram-+ve and Gram-ve bacteria. Its range includes staphylococci (but usually not streptococci) *E. coli*, *A. aerogenes*, *H. influenzae*, Friedländer's bacillus, pseudomonas and proteus. *M. tuberculosis* is also sensitive, but neomycin cannot be used in the treatment of tuberculosis because long-term therapy leads to toxic effects. The action is rapidly bactericidal and exudates, enzymes and by-products of bacterial growth do not inactivate neomycin. Resistance to this antibiotic rarely develops during treatment and organisms resistant to streptomycin are usually susceptible to neomycin. It is more active in alkaline than in acid media.

### ABSORPTION, FATE AND EXCRETION

Neomycin is not absorbed from the gastro-intestinal tract but it remains biologically active and leads to a marked suppression

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of coliform organisms in the bowel. Anaerobic organisms are not affected. The stools tend to become less odorous, loose and frequent. Given by intramuscular injection it is rapidly absorbed, widely distributed in the body tissues including the CSF, and it is excreted by the kidney.

### TOXIC EFFECTS

When given systemically neomycin gives rise to renal damage with proteinuria, oliguria and azotæmia. It also produces deafness and vestibular dysfunction. The severity of these side-effects depends upon the dose and the duration of treatment; the renal damage is usually reversible. For these reasons long-term therapy with neomycin in, for example, streptomycin-resistant tuberculous infection must not be employed. Large doses by mouth tend to be nauseating and the effect upon the bowel has already been mentioned. Serious enterocolitis due to overgrowth of resistant organisms is, however, rarely encountered. Applied to the skin and mucous surfaces it has little sensitising potency, so that allergic reactions are very uncommon.

### PREPARATIONS AND DOSES

Neomycin is used as the sulphate. It is assayed by conventional microbiological methods and contains not less than 600 Units per mg. For systemic use it is given by intramuscular injection: the adult dose is 10-15 mg. per Kg. of body weight daily in divided doses at 6-hourly intervals. A total daily dose of 1 G. must not be exceeded, and a course of treatment should not last for longer than 7 days. A 20-25 per cent solution is a suitable strength for intramuscular injection.

By mouth the usual dose is 1 G. every 4 hours, given as tablets each containing 500 mg.

Neomycin sulphate is available in a variety of proprietary preparations such as ointments and lotions for use on the skin, in wounds and in the eye. The usual strength of these preparations is 5 mg. per G. or ml. It is often combined with bacitracin and proprietary preparations containing corticosteroids are also available. Neomycin sulphate may also be injected into infected cavities, for example the pleural sac.

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### THERAPEUTIC USES

The main use of neomycin is in the treatment of bacterial infections of the skin where its rapid bactericidal action, low incidence of allergic dermatitis, and lack of production of resistant strains, make it a valuable therapeutic agent. It is useful in the prevention and treatment of secondary infection in burns and wounds, particularly when the infection is caused by the pseudomonas or proteus groups of organisms. It is also used in infections of the conjunctiva, cornea and eyelids.

By mouth neomycin is widely used to suppress the bowel flora before surgical operations upon the colon and it has been used successfully in the treatment of dysentery. In patients with hepatic cirrhosis oral neomycin is the antibiotic of choice in the prevention of hepatic coma. The neurological manifestations of severe hepatic disease are believed to be due in part to the absorption of nitrogenous products of protein breakdown, which gain access to the systemic circulation. Bacterial breakdown of protein plays an important part in the production of these substances and neomycin (along with a low protein diet) has been found to be the most successful antibiotic for long-term therapy in these patients.

For systemic use neomycin is restricted to severe infections with sensitive organisms which are not amenable to treatment with the more commonly used antibiotics. Provided the range of dosage indicated is not exceeded and the patient's renal function is normal the drug can safely be used in these circumstances.

### NOVOBIOCIN

Novobiocin is the approved name for an antibiotic produced by the growth of *Streptomyces niveus* and *Streptomyces spheroides*. It is an acidic substance and forms basic salts, pale yellow in colour, freely soluble in water, and stable.

### ANTIBACTERIAL ACTIONS

Novobiocin has a bactericidal action against Gram-+ve cocci and some Gram-—ve organisms including strains of pseudomonas

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and proteus. The coliform group are not affected. Although bacteria may be rendered resistant to novobiocin no cross-resistance with other antibiotics has been noted.

### ABSORPTION, FATE AND EXCRETION

Novobiocin is readily absorbed from the gastro-intestinal tract and peak blood levels after a single dose are reached in the plasma in 2-3 hours. Adequate concentrations of the drug persist for 8-12 hours or longer when repeated doses are administered. It diffuses into most of the body fluids but does not reach the CSF. The kidney excretes a proportion of the drug in active form but high concentrations are found in the bile and in the fæces.

### SIDE-EFFECTS

Novobiocin is well tolerated when given by mouth and gastro-intestinal upset is unusual, nor has serious supra-infection been noted. There is a rather high incidence of skin rashes and leucopenia, but these side-effects disappear when the drug is withdrawn. Some patients given large doses of novobiocin develop a yellow discoloration of the skin: this is attributable to the presence of a metabolic degradation product of the drug; it is not caused by a toxic effect upon the liver.

### PREPARATIONS AND DOSES

Proprietary preparations of novobiocin as tablets each containing 250 mg. and flavoured syrups for pædiatric use are available. The adult dose is 250-500 mg. every 6 hours or 0.5-1 G. at 12-hourly intervals. For a child 15 45 mg. per Kg. of body weight daily is the recommended dose.

### THERAPEUTIC USES

It would seem to be desirable to reserve novobiocin for use in severe infections resistant to other antibiotics or for patients who are sensitised to penicillin or the tetracyclines.

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### BACITRACIN

This antibiotic is produced in the growth liquor of the soil organisms *Bacillus licheniformis* and *Bacillus subtilis* var. *Tracy*. It is obtained as a buff-white, bitter, hygroscopic powder freely soluble in water; it deteriorates in aqueous solution at room temperature. Chemically it consists of polypeptides but its exact chemical constitution has not been determined. It is assayed by microbiological techniques and the BP 1958 prescribes activity of not less than 50 Units per mg. Bacitracin is rarely if ever used systemically nowadays and it is primarily of value as a local antibacterial agent.

#### ANTIBACTERIAL ACTIONS

Bacitracin has an antibiotic spectrum closely resembling that of penicillin, including Gram-+ve cocci and bacilli and a few Gram—ve organisms. In *experimental* syphilitic infections in rabbits it has a most remarkable potentiating effect upon penicillin, but it cannot be used in human infections because of its toxicity. Organisms which have become resistant to penicillin remain sensitive to bacitracin and it is not destroyed by penicillinase. It has, however, no action upon Gram—ve penicillinase-producing bacteria such as *E. coli*. Its antibacterial action is not inhibited by serum or inflammatory exudates. Resistance to bacitracin develops very slowly and has not proved to be a problem in clinical practice. Its mode of action is unknown.

#### ABSORPTION, FATE AND EXCRETION

Bacitracin is not absorbed in significant amounts from the gastro-intestinal tract and very little active drug is eliminated in the faeces. It is absorbed if given by intramuscular injection and some 30 per cent of the dose is eliminated in the urine. The rest is presumably destroyed in the body and it does not reach the CSF in significant amounts.

#### TOXICITY

Bacitracin is singularly free from toxic effects when used *locally*. It has a decided advantage over penicillin in that it rarely



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leads to skin sensitisation, and it can be applied to brain tissue and introduced into the spinal theca without causing serious irritation. On the other hand used systemically bacitracin is a toxic drug. In particular it produces acute renal tubular necrosis and fatalities have been reported from this cause. For this reason it is rarely, if ever, justifiable nowadays to use bacitracin for its systemic antibiotic effects. Lesser toxic effects recorded after systemic use include pain and induration at the injection site, skin eruptions, tinnitus and an unpleasant taste in the mouth.

### PREPARATIONS

For local use bacitracin is employed as an ointment or solution, the usual strength being 250-1,000 Units per G. or ml. The zinc salt which is more stable is also used and a number of proprietary preparations contain combinations of antibiotics and steroids for topical application.

### THERAPEUTIC USES

Bacitracin is applied locally in pyogenic skin infections, in burns and in infected wounds. It is also used in the eye, in ear infections, in dental sockets and in Vincent's stomatitis. By local infiltration it has been successfully used in the treatment of boils and carbuncles.

In meningitis it may be given intrathecally in solution in physiological saline. The strength should not exceed 1,000 Units per ml. and not more than 10,000 Units should be injected daily. A similar solution may be employed in brain abscess. Bacitracin has also been used by mouth in intestinal infections either alone or in combination with other antibiotics, but its value when used for this purpose is doubtful. As already indicated, bacitracin is not recommended for systemic use.

### POLYMYXIN B

Polymyxins comprise several antibacterial polypeptides produced during growth of different strains of *Bacillus polymyxa*. At least five fractions have been isolated but only polymyxin B is

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used in therapeutics, as it is less toxic than most of the other fractions.

### ANTIBACTERIAL ACTIONS

The spectrum of polymyxins is unique in that it is confined to Gram—ve bacteria. *Pseudomonas* is the most important susceptible organism from the clinical standpoint, but other Gram—ve organisms such as *E. coli*, *H. influenzae*, *klebsiella*, *shigella* and *aerobacter* are also susceptible. The antibiotic is bactericidal in low concentrations (0.05–0.2 microgram per ml.) and sensitive organisms show little tendency to become resistant to it. It retains its activity in the presence of pus.

### ABSORPTION, FATE AND EXCRETION

Polymyxin B is not absorbed when given by mouth and as might be expected from its peptide constitution it is largely destroyed in the gut. Nevertheless sufficient remains biologically active to suppress the Gram—ve intestinal flora.

After intramuscular injection it is readily absorbed and may be detected in the plasma for up to 12 hours. At low plasma levels very little appears in the urine, but with repeated doses leading to higher plasma concentrations substantial urinary excretion occurs. Eventually up to 50 per cent of the dose may be recovered in the urine. It is not excreted in the bile and does not diffuse into the CSF even when the membranes are inflamed. The rate of metabolic degradation requires that the drug be given every 4–6 hours to maintain bactericidal concentrations in the blood.

### TOXIC EFFECTS

Intramuscular injections of polymyxin are painful so that procaine is usually added in an attempt to reduce the discomfort. Fever may also follow the injection which in fact contains a "foreign protein".

The main toxic effect of polymyxin is unpleasant paræsthesia involving the extremities, the scalp, face and mouth; and this may occur with conventional systemic doses. Circumoral flushing accompanies these symptoms but objective evidence of sensory loss is usually lacking. After larger doses, vertigo, dysarthria and

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ataxia have been noted. These disturbances disappear when the drug is withdrawn. They are not seen when polymyxin is given by mouth or by intrathecal injection. Other polymyxin fractions which were used initially gave rise to a high incidence of renal toxicity with albuminuria, oliguria and nitrogen retention. Polymyxin B is less toxic in this respect, but not entirely harmless. The urine should be examined frequently and the serum urea and electrolytes estimated when the drug is used systemically. Particular care is needed in patients who have evidence of impaired renal function. Oral and intrathecal administration of polymyxin B are not usually followed by important side-effects, and it can be applied to the skin with little risk of sensitisation reactions.

### PREPARATIONS AND DOSES

Polymyxin B is used as the Sulphate which is the official preparation. It is a freely soluble, white powder, stable in the dry state and in solution if it is stored at 4° C. It contains not less than 6,000 Units per mg. and is assayed by the usual microbiological methods employed in antibiotic assay. The usual doses are as follows. For systemic effects given intramuscularly 200,000–250,000 Units at 4- or 6-hourly intervals. The injection is made up in 1 per cent sterile procaine solution. The maximum daily dose should not normally exceed 1,250,000 Units. For a child 10,000–20,000 Units per Kg. of body weight daily is a suitable dose.

*By intrathecal injection* 20,000–100,000 Units once or twice daily may be given in sterile physiological saline depending upon the age of the patient.

*For local application* 0.1 per cent in solution may be used; and a variety of proprietary preparations containing polymyxin B and other antibiotics with corticosteroids are available.

If polymyxin is given by mouth as an intestinal antiseptic 1 million Units thrice daily is the usual dose.

### THERAPEUTIC USES

The prime indication for use of polymyxin B is in the treatment of pseudomonal infection including septicæmia, urinary tract infections and meningitis. These infections are often resis-

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tant to other antibiotics. It is also used in other resistant Gram—ve infections, particularly Gram—ve meningitis, which have failed to respond to streptomycin, chloramphenicol, tetracyclines and sulphonamides. It may be applied to the skin and to wounds either alone or combined with other antibiotics when mixed infection is present. It has also been used in intestinal infections due to Gram—ve organisms.

### VANCOMYCIN

This new antibiotic is obtained from *Streptomyces orientalis*. It acts primarily against Gram-+ve bacteria and is bactericidal. *Staphylococcus aureus* is particularly sensitive to its action and it shows no cross-resistance with other antibiotics. Only actively multiplying organisms are killed by vancomycin and resistance to its action is slow to develop. It is not appreciably absorbed from the gastro-intestinal tract, but large amounts of active drug appear in the faeces when it is given by mouth; the Gram-+ve intestinal flora are markedly suppressed but Gram—ve organisms are not affected. Administered intravenously it diffuses into serous cavities but not into the CSF, and it is excreted in large amounts in the urine. Toxic effects so far reported in man include phlebitis at the site of intravenous injection, drug fever, skin eruptions and deafness (nerve deafness). Vancomycin has been used successfully in the treatment of severe resistant staphylococcal infections, especially staphylococcal endocarditis, a condition in which bacteriostatic antibiotics are ineffective. Staphylococcal enterocolitis has been cured by oral treatment with the drug. The suggested dose is 0.5 G. every 6 hours by intravenous injection; and the same dose is given by mouth for a local effect in the bowel in staphylococcal enteritis.

### RISTOCETIN

Ristocetin is a new antibiotic produced by the growth of a species of actinomycetes named *Nocardia lurida*. Its antibacterial spectrum is similar to that of vancomycin and it has been used in the treatment of resistant staphylococcal infections. Ristocetin can only be administered intravenously in a total daily dose of

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25-75 mg. per Kg. of body weight. Side-effects include thrombophlebitis at the injection site, drug fever, skin eruptions and leucopenia.

### VIOMYCIN

This antibiotic is obtained from certain strains of *Streptomyces puniceus*, and it is a pale-yellow hygroscopic substance soluble in water.

It exhibits bacteriostatic activity against *M. tuberculosis* including strains resistant to streptomycin. Resistance to its action develops *in vivo* but this can be retarded by combined therapy with other tuberculostatic drugs.

It is not absorbed when given by mouth and is therefore administered by intramuscular injection. It diffuses poorly into serous cavities and does not reach the CSF. It is excreted in the urine. Viomycin is more liable than is streptomycin to produce toxic effects, namely—renal damage, electrolyte disturbances, vestibular dysfunction and deafness. It also gives rise to allergic reactions. The severity of these side-effects is proportional to the dose employed and its low therapeutic ratio makes the clinical usefulness of viomycin very limited. Viomycin is used as the sulphate and is dispensed in sealed phials each containing the equivalent of 1 G. of viomycin base. The dose is 1-2 G. by deep intramuscular injection twice weekly. Its sole use is in the treatment of tuberculosis, and only when the infecting organism is resistant to the standard remedies. Combined therapy with a chemotherapeutic agent to which the organism remains sensitive is essential.

### CYCLOSERINE

This antibiotic is obtained from *Streptomyces orchidaceus* and *Streptomyces garyphalus*. It is described chemically as 4-amino-isooxazolidin-3-one and is manufactured synthetically.

Cycloserine has a bacteriostatic action upon *M. tuberculosis* and some Gram—ve and Gram+ve bacteria. Tubercle bacilli become resistant to it but it does not show cross-resistance with other antituberculous agents.

This drug is readily absorbed from the gastro-intestinal tract and diffuses throughout the body fluids including the CSF. It is

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excreted slowly by the kidney so that when doses of more than 1 G. daily are given cumulation tends to occur. This gives rise to a high incidence of unpleasant toxic effects mainly involving the central nervous system. These include drowsiness, headache, involuntary muscular twitching and (in some patients) convulsions and frank psychotic behaviour. It also produces allergic skin reactions. Cycloserine is dispensed in tablets or capsules each containing 250 mg. The daily dose must not exceed 1 G. The usual justification for its use in therapeutics is as an alternative remedy in the treatment of resistant tuberculous infection, combined with other tuberculostatic drugs. The patient should be under close medical supervision. Exceptionally, it may be of value in urinary tract infections resistant to all other chemotherapeutic agents.

### TYROTHRIN

Tyrothricin is not of great therapeutic value, but it is of historic interest as it was the first antibiotic to be obtained from a culture of soil organisms. It was isolated in 1939 by Dubos from *Bacillus brevis*, an aerobic soil organism. Tyrothricin is a mixture of polypeptides and contains two main fractions named gramicidin and tyrocidine, which are also polypeptide mixtures. Tyrothricin is an off-white powder insoluble in water but so stable that it may be autoclaved without destruction.

The antibiotic has bacteriostatic and bactericidal properties against Gram-+ve organisms, notably streptococci; the tyrocidine fraction has weak Gram—ve activity but this is not sufficient to be of value in Gram—ve infections. Gramicidin is weight for weight much more powerful than tyrocidine against organisms sensitive to both fractions. Sensitive organisms do not become resistant to tyrothricin but its antibacterial action is inhibited to some extent by pus and serous exudates. Tyrocidine acts as a disinfectant: it completely inhibits the oxidation-reduction systems of bacterial cells, and it exerts a lytic effect. Gramicidin on the other hand has no lytic properties but it prevents normal bacterial carbohydrate metabolism, so that growth and division cease.

Tyrothricin cannot be used for systemic infections as not only

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is it inactivated in the blood by plasma globulins, but it also produces hepatic necrosis and hæmorrhagic visceral lesions. Applied locally it is relatively non-toxic, does not interfere with healing, and sensitivity reactions are very uncommon. It must not, however, be used in wounds or cavities if there is any possibility that it may reach the subarachnoid space, as severe chemical meningitis has resulted. Prolonged application to the nasal mucosa has caused loss of the sense of smell.

Tyrothricin is normally prepared for use in an ointment or as a solution. The usual strength is 0.5 mg. per G. or ml., but more dilute solutions—1 in 5,000—are used in the eye. Proprietary preparations in which tyrothricin is compounded with other antibiotics and preparations employing the gramicidin fraction are also available commercially. Lozenges may be used in mouth and throat infections.

The clinical usefulness of tyrothricin is limited by its narrow antibacterial spectrum, but it is of value in indolent skin infections due to Gram-+ve cocci and in chronic marginal corneal ulcers.

## FRAMYCETIN

Framycetin is obtained from a strain of *Streptomyces decaris*. It is a bacteriostatic and bactericidal antibiotic effective in Gram-+ve and Gram-—ve infections; staphylococci, proteus and pseudomonas are particularly susceptible to its action. It is used exclusively as a topical application and it is well tolerated. Sensitivity reactions have not been reported.

Framycetin sulphate is the preparation employed either as an ointment or solution, and the usual strength is 1.5 per cent. It is employed in the treatment of staphylococcal skin infections and mixed infections due to proteus and pseudomonas.

## NYSTATIN

Nystatin is produced by the growth of *Streptomyces noursei*. It is obtained as a yellow, insoluble powder which retains its activity for several months stored at 4° C.

This antibiotic has no antibacterial actions, but is active *in vitro* against a variety of fungi including *Candida albicans*, cocci-

## ANTIBACTERIAL AGENTS

*dioides* and *histoplasma*. It exerts a fungistatic or fungicidal action depending upon the concentrations used.

Nystatin is not destroyed in the gastro-intestinal tract but very little is absorbed into the blood-stream, and the major portion ingested is excreted in the fæces. Because of its irritant properties it cannot be given parenterally. Its value in systemic mycotic infections is therefore very limited.

Applied locally, nystatin is well tolerated and reactions are rare. Large doses by mouth produce nausea, vomiting and diarrhœa.

Nystatin is available commercially as an ointment containing 100,000 Units per G. and as tablets containing 100,000 Units in each—for local use in the vagina or anal canal. Tablets for oral use containing 500,000 Units in each are also available.

Nystatin is used locally in the treatment of moniliasis, especially *Candida albicans* infections. Good results are obtained in oral thrush, intestinal, vaginal, anal, and cutaneous moniliasis. Large doses by mouth have also been tried in systemic fungus infections but—as might be expected from its poor absorption—disappointing results have been obtained.

## FUMAGILLIN

This antibiotic is produced by the growth of *Aspergillus fumigatus*, and it is an organic acid ester. It has no useful antibacterial actions, but *in vitro* it is amœbicidal against *Entamœba histolytica*, in high dilution. The encysted stage of the parasite is more susceptible than the vegetative form, and resistance to its action has not been noted during treatment. Fumagillin is not well absorbed from the gut and toxic effects are usually confined to gastric intolerance. Large doses may, however, produce dermatitis and leucopenia. The recommended therapeutic dose is 10–20 mg. thrice daily by mouth for 10–14 days.

Fumagillin has been used in the treatment of chronic drug-resistant intestinal amœbiasis and favourable results—indicated by the clearance of cysts from the stools—have been reported. It is not recommended for acute amœbic dysentery and it is of no value in the treatment of amœbic hepatitis.



## PUROMYCIN

This antibiotic, obtained from *Streptomyces alboniger*, is a complex purine derivative. Tested in the laboratory it is active against *Entamoeba histolytica* and various species of trypanosome. Clinical trials of this antibiotic have been carried out in amœbiasis with generally unsatisfactory results.

## CHEMOTHERAPY OF TUBERCULOSIS

Streptomycin is the antibiotic of choice in the treatment of tuberculosis; this preparation and other antibiotics of limited value in the treatment of resistant infections have already been described. The following paragraphs deal with the remaining chemotherapeutic agents used in tuberculosis; and schemes of dosage favoured at the present time are mentioned.

## SODIUM AMINOSALICYLATE

Sodium Aminosalicylate is the sodium salt of para-aminosalicylic acid (PAS). This acid was shown to have tuberculostatic activity by Lehmann, who tested a large number of similar compounds; the earlier observation by Bernheim that both benzoic and salicylic acids increased the oxygen uptake of tubercle bacilli was the starting point for Lehmann's work. The sodium salt is a white crystalline powder freely soluble in water and with a sweet, nauseating taste. It is used instead of the acid as it is less likely to induce vomiting.

**ANTIBACTERIAL ACTIONS.** Aminosalicylate inhibits the growth of virulent tubercle bacilli *in vitro*; the effect is remarkably specific, being confined to this species. The action is tuberculostatic and *in vitro* concentrations of the order of 1 microgram per ml. are inhibitory. The drug is active in the presence of serum but is inhibited by high concentrations of salicylic acid, pantothenic acid and PABA. A large inoculum of tubercle bacilli markedly diminishes its tuberculostatic action. *In vivo* it is much less effective than either streptomycin or isoniazid. Resistance to its action develops both *in vitro* and *in vivo* but more slowly than to strep-

tomyacin; combined therapy prevents the development of resistance to either drug and this is also the case when sodium aminosalicylate is used along with isoniazid.

It is worthy of note that aminosalicylate lacks the analgesic and antipyretic properties of salicylates; and the symptoms and signs of "salicylism" do not develop even with the large doses regularly used in therapeutics.

*Absorption, Fate and Excretion.* Aminosalicylate is readily absorbed from the small intestine and after a single dose peak blood levels are reached in under 2 hours. The drug is widely distributed in the tissues but does not penetrate into the CSF. Plasma levels decline rapidly so that negligible concentrations of the drug remain after 8 hours. This is due to rapid excretion by the kidney both by glomerular filtration and tubular excretion. Some 80 per cent of the ingested dose may be recovered in 10 hours. Tubular blocking agents such as probenecid have been shown to delay the excretion. A variety of excretory products have been identified, the largest fraction being acetylated. It follows that in order to maintain continuous bacteriostatic plasma levels, aminosalicylate must be given at 6-hourly intervals, and this is routine practice when it is combined with streptomycin. Clinical experience has shown, however, that when it is combined with isoniazid administration twice daily gives satisfactory results.

*Toxic Effects.* Aminosalicylates are gastro-intestinal irritants and the large doses employed produce nausea, abdominal discomfort, vomiting and loose stools. Measures to minimise these troublesome side-effects are mentioned in the section on preparations and doses. Of more serious import is the development of sensitisation to the drug. The clinical features include drug fever, dermatitis, lymphadenopathy and occasional jaundice. These subside when the drug is withdrawn and recur if it is given again. Sometimes desensitisation may be successfully accomplished by using very small doses of aminosalicylate and gradually increasing the dose until the therapeutic range is reached, under antihistaminic or steroid cover.

Proteinuria and hæmaturia have been reported during amino-

salicylate therapy. These complications are attributable to renal irritation by the drug and its excretory products. Occasionally serious water and electrolyte depletion with oliguria and nitrogen retention have been noted. This is due to vomiting, diarrhoea and loss of fixed base in the urine along with the large amounts of the drug being excreted. A contributory factor is the use of liquorice as a flavouring agent to disguise the taste of the drug, as this has been shown to promote the renal excretion of potassium. Long-term therapy with aminosaliclylate may also lead to hypoproteinaemia—an action which is comparable to the effects of high dosage with salicylates. It may be corrected with Vitamin K. Long-term treatment with aminosaliclylate produces goitre and hypothyroidism. It acts by preventing the incorporation of iodine into the tyrosine molecule to form thyroxine. The administration of thyroid or thyroxine but not iodine, prevents the development of both goitre and hypothyroidism. There is also evidence that aminosaliclylate can produce psychotic symptoms; these have been noted both during the early stages of therapy and after a delay of several months. They are of rare occurrence.

*Preparations, Administrations and Doses.* The standard drug is Sodium Aminosaliclylate given by mouth as cachets, tablets or in a flavoured mixture. The last preparation is the most reliable in securing complete absorption of the drug, but it is also much more likely to produce gastro-intestinal intolerance. Cachets are usually preferred and each contains 1.5 G. of the drug. The official Tablet contains 0.5 G. in each. Proprietary preparations containing sodium aminosaliclylate as enteric-coated tablets or granules are less likely to cause gastric intolerance but have the disadvantage of irregular intestinal absorption. Para-aminosalicylic acid and its potassium salt have no advantages over the standard remedy and Calcium Benzamidosaliclylate is a newer preparation not yet fully assessed.

Sodium Aminosaliclylate should be given as far as possible along with or immediately after food and it is often helpful to begin treatment with relatively small doses, gradually increasing to the full dose by the end of one week. This helps to avoid gastro-intestinal intolerance. The recommended daily doses are as

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follows: If used in combined therapy with streptomycin 5 G. four times daily; if used with isoniazid 5 G. twice daily suffices. For a child 0.5 G. per Kg. of body weight per day if used with streptomycin; 0.35 G. per Kg. of body weight per day with isoniazid.

**THERAPEUTIC USES.** Sodium aminosalicylate is one of the three standard chemotherapeutic agents used in the treatment of tuberculosis. Further details are given later in this chapter. It has also been used in the treatment of leprosy in patients who are excessively sensitive to the toxic effects of the sulphones, but it is relatively ineffective in this disease.

### ISONIAZID

Isoniazid, described chemically as isonicotinic acid hydrazide or pyridine-4-carboxyhydrazide, is one of the three standard drugs used in the treatment of tuberculosis. It is an almost white, odourless, crystalline compound with an initial sweetish taste and a bitter after-taste. It is soluble in water.

**ANTIBACTERIAL ACTIONS.** The action of isoniazid is specifically against *M. tuberculosis*, and *in vitro* this action is apparent in dilutions as low as 0.05  $\mu$ g. per ml. Tested in this way it is many times more effective than either streptomycin or sodium aminosalicylate. The effect is delayed for one or two cell divisions and is initially bacteriostatic and later bactericidal. Susceptible tubercle bacilli bind isoniazid; and it seems likely that the action of the drug is due to interference with the formation of an essential metabolite, which has not yet been identified. Resistance to the action of isoniazid develops both *in vitro* and *in vivo* more rapidly than to streptomycin. In practice this can be prevented by concomitant therapy with streptomycin or aminosalicylate. No other important pharmacological actions have been demonstrated by routine investigations in animals.

**Toxic Effects.** There is general agreement that isoniazid therapy is relatively free from side-effects when doses of 200 mg.

daily are used in adults. Some patients may experience dryness of the mouth, anorexia, nausea and constipation during the early weeks of treatment, but these symptoms do not necessitate interruption of therapy. Headache, dizziness, drowsiness and difficulty in starting micturition may also occur; twitching of the lower limbs with exaggerated tendon reflexes have also been recorded.

Allergic reactions to isoniazid are rare but drug fever, dermatitis, lymphadenopathy, jaundice and bone marrow depression are on record. Other serious complications include peripheral neuropathy, convulsions and psychotic manifestations. These are more likely to occur if doses in excess of 5 mg. per Kg. body weight daily are used; and a history of epilepsy or mental disturbance is often obtained from patients who develop convulsions or become psychotic during isoniazid therapy. Peripheral neuritis may persist after the drug is withdrawn and in some patients permanent disability has resulted. It has been claimed that adequate supplements of pyridoxine and other vitamins of the B group may help to prevent these nervous disturbances. A small number of patients become euphoric, and withdrawal symptoms have been described when treatment is terminated.

*Absorption, Fate and Excretion.* Isoniazid is rapidly absorbed after oral administration, with peak blood levels 1-2 hours later. After 6 hours the plasma level has fallen by half, but traces are still found in the blood up to 24 hours after the last dose. The drug diffuses freely, reaching the CSF and serous cavities, and it also penetrates into caseous tuberculous lesions. It is degraded to isonicotinic acid and acetylated compounds which are excreted in the urine. Very little unchanged isoniazid appears in the urine.

*Preparations and Doses.* Isoniazid is given by mouth as Tablets each containing 50 mg. Proprietary cachets containing the appropriate dose of both isoniazid and sodium aminosalicylate are also employed. The daily dose is 200 mg. given as 100 mg. twice daily for an adult, and for a child 3-5 mg. per Kg. body weight daily. A total daily dose of 10 mg. per Kg. body weight is used in the treatment of tuberculous meningitis.

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*Uses.* Isoniazid is used, combined with other drugs, in the treatment of tuberculosis and the recommended combinations are given on p. 488.

### RELATED COMPOUNDS

A number of drugs chemically related to isoniazid have been used in the treatment of tuberculosis. Generally, they are all more toxic than isoniazid and are not in common use. The best known is Iproniazid—the *iso*-propyl derivative—which is a potent tuberculostatic agent. Organisms resistant to isoniazid are also resistant to iproniazid, and a higher incidence of side-effects attends its use. For these reasons it is not now employed in the treatment of tuberculosis. Iproniazid is of pharmacological interest as it has been shown to be a powerful inhibitor of monoamine oxidase, an action not seen with isoniazid. This property makes iproniazid a useful “research tool” in experimental pharmacological investigations in animals. The drug has also been found, empirically, to reduce the frequency of attacks of angina pectoris in patients with ischaemic heart disease, but its toxic potentialities make it unsuitable for long-term use in this condition. Its mode of action in angina pectoris is unknown.

*Pyrazinamide.* This drug, pyrazine-2-carboxyamide, has undergone clinical trial combined with isoniazid in pulmonary tuberculosis. A high incidence of hepatitis, which has proved fatal in some patients, has discouraged its use in therapeutics.

**COMBINED THERAPY OF TUBERCULOSIS.** A detailed account of the management of patients with the various forms of tuberculosis is beyond the scope of this book and should be sought in standard textbooks of therapeutics. The following paragraphs deal with the antituberculous drug combinations which have been found to be effective. For all cases prolonged treatment for at least one year is required, and samples of infected material should be collected for culture and for determination of drug-sensitivity before treatment is begun and also at intervals during therapy.

In young patients, streptomycin 1 G. daily given as a single

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injection and isoniazid 100 mg. twice daily is the most effective drug combination. Patients over the age of forty who receive streptomycin *daily* may develop labyrinthine disturbance, and in these patients 1 G. *thrice weekly* is used. If this is done, isoniazid in the above-mentioned dosage and sodium aminosalicylate 5 G. twice daily must also be given, otherwise in a proportion of patients a strain of tubercule bacilli resistant to isoniazid will emerge. Later, streptomycin therapy may be stopped and treatment continued with daily isoniazid and aminosalicylate in the doses mentioned above. The latter combination may be used from the start in the management of less acute forms of the disease.

Daily streptomycin with aminosalicylate (20 G. daily) may be used as an alternative combination but the large daily dose of aminosalicylate necessary to prevent the emergence of streptomycin resistance is not readily tolerated. Hence the combination is not used so often nowadays.

In tuberculous meningitis a different scheme of therapy is used initially, as of the three standard remedies only isoniazid reaches the CSF. Streptomycin is given daily in the usual dose by intramuscular injection and it is also injected intrathecally once a day; 25 100 mg. is used depending upon the age of the patient. At the same time, sodium aminosalicylate 10 G. daily and isoniazid 10 mg. per Kg. body weight daily are given by mouth. Streptomycin therapy needs to be continued for one week only, and the dose of isoniazid may be reduced to 3-5 mg. per Kg. daily at the end of 6 months.

Patients in whom the infecting organism is resistant to the standard remedies present special problems. They require treatment with alternative remedies—usually Viomycin and Oxy-tetracycline. They should be under the close supervision of a physician experienced in the management of such cases.

## CHEMOTHERAPY OF LEPROSY

The drugs of choice in the treatment of leprosy are the sulphones, which have largely replaced the time-honoured remedies—chaulmoogra and hydnocarpus oils. These drugs along with

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thiacetazone (an alternative drug for occasional use) are described in this section. Streptomycin and sodium aminosalicylate, which are much less effective than the sulphones, are sometimes used as supplements and for the treatment of patients who are abnormally sensitive to the toxic effects of the sulphones. They are not discussed further in relation to leprosy.

The investigation of new drugs of potential value in leprosy presents many difficulties. *Mycobacterium lepræ*, the organism of human leprosy, has not yet been successfully cultured on artificial media nor has the human form of the disease been transmitted to experimental animals. Furthermore, the results of chemotherapeutic investigations in murine leprosy (the type of disease occurring as a natural infection in rats) do not necessarily coincide with the results of therapy in human patients. For these reasons and others, the sulphones whose antibacterial properties have been recognised for over twenty years, have only recently become firmly established as valuable chemotherapeutic agents in leprosy.

### SULPHONES

The sulphones comprise a number of drugs chemically related to the sulphonamides. Two are official, namely Dapsone and Solapsonone, and they are described as representative of the group

DAPSONE is diaminodiphenylsulphone (DDS), a white crystalline powder insoluble in water. It is the parent substance and other sulphones are amino-substituted derivatives.

*Antibacterial Actions.* The antibacterial spectrum of dapsone resembles that of the sulphonamides and its action is likewise antagonised by PABA. Clinically its use is restricted to the treatment of leprosy in which its mode of action has not been determined. It would appear that resistance to its actions does not develop.

*Toxic Effects.* Dapsone therapy gives rise to a variety of side-effects, especially if daily treatment is given. Anorexia, nausea, vomiting and giddiness are not uncommon when treatment is first begun, but these symptoms do not usually demand interrup-



tion of therapy. Cyanosis due to methæmoglobinæmia may also occur in the early stages of treatment but usually disappears with continued therapy. Mild anæmia develops as a rule early during the course of therapy. This has generally been regarded as hæmolytic in type, and the hæmoglobin level rises spontaneously with continued treatment. Severe acute hæmolytic anæmia has been reported on rare occasions. A depressive mental illness sometimes occurs but is uncommon when twice-weekly dosage is used. About 2 per cent of patients develop sensitisation to sulphones with drug fever, dermatitis, lymphadenopathy and hepatitis. Lepra reactions, that is to say reactivation of leprosy lesions akin to the Herxheimer reaction, are also induced by dapsone. These may be severe and when they involve peripheral nerves they may be intractable. Reduction of dosage and cautious treatment with steroid hormones have proved valuable in the control of these distressing side-effects.

*Absorption, Fate and Excretion.* Dapsone is well absorbed from the gut with peak blood levels about 2 hours after the dose has been given. The drug is fairly evenly distributed throughout the body but does not readily enter the CSF. 50-80 per cent of the dose can be recovered in the urine partly unchanged and partly conjugated. Excretion takes place slowly and after prolonged treatment dapsone can still be detected in the urine for some 14 days after the last dose. This fact readily explains the ease with which cumulation and an increased incidence of toxic effects occur with daily administration.

*Preparations and Doses.* Dapsone is usually given by mouth in tablets each containing 100 mg. It has also been administered by subcutaneous injection as a 25 per cent suspension in arachis oil. The dosage schedules employed in leprosy are mentioned below.

**SOLAPSONE.** This drug is a complex tetrasulphonate of dapsone, obtained as a white, amorphous powder freely soluble in water. In common with other sulphones in which both amino groups are substituted, solapsone is itself inactive, but it dissociates into active compounds in the body.

*Toxic Effects.* With oral administration the toxic effects of solapsone are those of dapsone which is released in the gut. Parenterally, solapsone is relatively free from side-effects but they are similar to those produced by dapsone.

*Absorption, Fate and Excretion.* Solapsone is poorly absorbed from the intestine and over 80 per cent of the dose is excreted in the faeces. A small proportion is hydrolysed to dapsone which is then absorbed. Thus, the effects of oral solapsone are due to dapsone. Given by parenteral injection solapsone is partly converted to monosubstituted sulphones and it is believed that these metabolites are active against the leprosy bacillus; only traces of dapsone are produced. Solapsone and its metabolites are excreted in the urine more rapidly than dapsone. .

*Preparations and Doses.* Solapsone is available as tablets each containing 0.5 G. The official daily dose is 1-3 G. It is now more usually given by subcutaneous or intramuscular injection as a 50 per cent aqueous solution—Strong Injection of Solapsone. The dose is 1-2.5 G. twice weekly.

**THIACETAZONE.** This drug, one of a group of compounds known as thiosemicarbazones, is a pale-yellow, insoluble crystalline powder. Toxic effects include allergic dermatitis and lepra reactions; more serious is the occurrence of bone marrow depression with severe anæmia and agranulocytosis. Fatal hepatitis has also been reported. Thiacetazone was originally introduced for the treatment of tuberculosis, but it is now mainly used in the treatment of leprosy. It is less effective than the sulphones and is best reserved for patients in whom sulphones produce serious toxic effects. It is given by mouth as tablets each containing 25 mg. in a daily dose of up to 200 mg.

**CHAULMOOGRA AND HYDNOCARPUS OILS.** These oils have been used in the treatment of leprosy for centuries. They are obtained by expression from the seeds of various species of *Hydnocarpus*, trees indigenous to Burma and other Eastern countries. The active principles are unsaturated cyclic fatty acids,

and the oils are used as such or in the form of ethyl esters. The oil, or its esters, is usually given by direct infiltration of the leproma by multiple intradermal injections, combined with intramuscular injections once or twice weekly. The injections are painful, but dilution with olive oil and the addition of camphor or creosote to the mixture reduces the pain. Serious systemic reactions are uncommon. These oils have been replaced by the sulphones in modern therapeutics, but they are still used in endemic areas in the East, where their low cost and easy availability frequently dictate their use.

**DRUG TREATMENT OF LEPROSY.** Dapsone is the drug of choice given by mouth in an initial dose of 25–50 mg. twice weekly. The dose is increased by 50–100 mg. every month to a maximum of 200–400 mg. twice weekly. Alternatively, Solapsonc may be used, preferably by intramuscular injection. The initial dose is 1 G. gradually increasing to a maximum of 2.5 G. twice weekly. Gradual increase in the dose in this manner leads to a lower incidence of serious side-effects. Most physicians experienced in the treatment of leprosy recommend that ferrous sulphate and vitamins of the B group be given along with sulphone therapy. Treatment must be prolonged for years and even then relapse may occur when therapy is discontinued.

Thiacetazone is generally reserved for patients who show serious intolerance to the sulphones. The results of long-term therapy with this drug are less satisfactory than with dapsone, and the possibility of agranulocytosis makes it unsuitable for mass treatment. Streptomycin and sodium aminosalicylate are sometimes used as supplements, or when dapsone is temporarily withdrawn because of intolerance. As mentioned above, chaulmoogra and hydnocarpus oils are used nowadays only in areas where the more effective remedies are not freely available.

Dapsone is also effective in controlling dermatitis herpetiformis but most dermatologists prefer to use sulphapyridine.

## THE SULPHONAMIDES

The sulphonamides were introduced into clinical practice nearly twenty-five years ago and were the first really effective agents in the treatment of systemic bacterial infections in man. In recent years they have been largely replaced by the antibiotics, and there are comparatively few infections in which sulphonamides are now the treatment of choice. Nevertheless, the sulphonamides are of great historic interest; they also illustrate certain classic concepts of drug action and important therapeutic principles. These drugs are therefore discussed here at greater length than is perhaps warranted by their status in clinical practice today.

*Chemistry.* The basic chemical structure of the antibacterial sulphonamides is *para*-aminobenzenesulphonamide—sulphanilamide. The structural formulæ of this drug and the other important sulphonamides are shown in Appendix II. It will be seen that the sulphonamides employed in therapeutics are obtained by substitution of one hydrogen atom in the amide group or alternatively in the *para*-amino group. (Substitution in the latter group generally yields compounds of low antibacterial activity *in vitro*, but *in vivo* the active component is released.) As far as structure-activity is concerned, the free  $\text{NH}_2$  grouping is essential and those drugs in which substitution is made in this grouping, depend upon the release of the active component *in vivo*. The  $\text{SO}_2\text{NH}_2$  group is not itself essential but it is important that the S atom be directly attached to the benzene ring.

Substitution of heterocyclic aromatic nuclei, for example pyrimidine in the  $\text{SO}_2\text{NH}_2$  group, yields the most active compounds and it seems likely that maximum antibacterial activity is present in this compound—that is, sulphadiazine. Further substitution has, however, given drugs with pharmacological properties more favourable than those of sulphadiazine (for example solubility in acid urine) without sacrificing high antibacterial activity.

## EFFECTS ON MICRO-ORGANISMS

(1) *Antibacterial Spectrum.* The sulphonamides are active against a wide range of micro-organisms. Highly susceptible bacteria include *meningococcus*, *Shigella dysenteriae*, *Streptococcus  $\beta$ -haemolyticus* and *pneumococcus*. *E. coli*, *gonococcus*, *Kl. pneumoniae*, *H. influenzae*, *H. ducreyi*, *Pasteurella pestis*, *V. cholerae*, *B. anthracis*, and the viruses of lymphogranuloma inguinale, trachoma and psittacosis are also generally susceptible. More resistant but still amenable to treatment are some strains of *clostridium*, *Staphylococcus pyogenes*, *actinomyces*, *brucella*, *A. aerogenes* and *Proteus vulgaris*. Other organisms are generally only slightly sensitive or are so resistant that sulphonamides are not effective. It should be emphasised that with the notable exception of the *meningococcus*, all other sulphonamide-sensitive organisms are capable of developing resistance to sulphonamides: many strains are now unaffected by these drugs. The action of sulphonamides in the concentrations readily obtainable *in vivo* is bacteriostatic rather than bactericidal and the final eradication of infection is dependent upon the natural defence mechanisms of the patient. These responses in the host are not influenced by sulphonamides, but when bacterial growth is inhibited by these drugs phagocytosis is facilitated. In urinary tract infections sulphonamides may be bactericidal because of the high concentration of the drug attained during its excretion in the urine.

(2) *Mode of Action.* It is generally agreed that sulphonamides exert their bacteriostatic effects by antagonising the action of *para*-aminobenzoic acid (PABA) which is an "essential metabolite" for sulphonamide-sensitive organisms. This theory was first proposed by Wood and Fildes and now bears their name. It has been further elaborated to suggest that organisms which synthesise folic acid (which contains a PABA radical) are sensitive to sulphonamides while those which can utilise preformed folic acid, or do not require it, are unaffected by sulphonamides. The similarity in chemical structure between PABA and sulphonamides is an essential part of the hypothesis; and this similarity of structure accounts for the phenomenon of "competition" readily demonstrated *in vitro* over wide molar concentrations. There is

a time-lag—for the occurrence of several cell divisions—before bacterial multiplication is inhibited by sulphonamides, presumably because the bacterium has a store of folic acid and the pharmacological action begins only when this store is no longer available to a new generation of bacteria. Although this explanation may not account for all of the antibacterial actions of sulphonamides it is certainly fundamental in the pharmacological mechanisms involved. Other drugs, which contain PABA (notably procaine and related local anæsthetics), also antagonise the actions of sulphonamides, a fact of some practical importance. The presence of pus and necrotic tissue also interferes with their action.

(3) *Acquired Bacterial Resistance.* As noted above micro-organisms initially sensitive to sulphonamides readily acquire resistance to them both *in vivo* and *in vitro*. With the exception of the meningococcus, which does not become resistant, all the pyogenic cocci and Gram-negative bacilli show this phenomenon and it has also been noted in the larger viruses. Acquired resistance is important in therapeutics because it limits the usefulness of sulphonamides, especially in infections caused by gonococci, *Shigella dysenteriae* and *Staphylococcus pyogenes*. Resistance is more readily developed to the less potent sulphonamides such as sulphanilamide than to the more effective pyrimidine derivatives, and it is also favoured both *in vivo* and *in vitro* by exposure of the organism to inadequate concentrations of the drug. Cross-resistance between members of the sulphonamide group of drugs is the rule, but acquired sulphonamide resistance does not mean that the organism has also become resistant to penicillin or other antibiotics. Bacteria can readily be made to acquire the maximum degree of resistance; that is to say, progressively increasing the concentration of sulphonamide in the culture medium ceases, at a certain point, to create a greater degree of resistance. Once resistance has developed it is usually permanent, and such organisms remain resistant through many animal passages and after prolonged subculture. However, organisms in which maximal resistance has not developed may regain full sensitivity if cultured in a sulphonamide-free medium. This presumably

accounts for the fact that many strains of gonococci isolated from patients with acute gonococcal urethritis are now fully sensitive to sulphonamides, whereas a decade ago the majority of strains showed sulphonamide resistance. In the intervening years penicillin has been used exclusively in the treatment of this condition. A further example of sulphonamide resistance may be cited. At the present time in this country a high percentage of strains of *Shigella sonnei* isolated from patients with bacillary dysentery are sulphonamide-resistant, whereas formerly the majority of strains were susceptible. Presumably this is due to the use of sulphonamides over many years in this condition.

The emergence of resistant organisms appears to be due to chance mutation, giving rise to resistant variants which are then favoured as the sensitive organisms are destroyed by the bacteriostatic drug, and *in vivo* by the natural defence mechanisms of the body. The resistant variants may be present in the bacterial population before exposure to the drug or they may arise during treatment with the sulphonamide. The very rapid life-cycle of bacteria allows such mutations to occur frequently and in a matter of days or a few weeks the entire group may become resistant. The various mechanisms of "drug-fastness" have not yet been satisfactorily explained on a biochemical basis and the student should refer to the standard works on bacteriology for further discussion.

As far as prevention of drug resistance is concerned, the most important factors are restriction of the use of sulphonamides to those occasions when a susceptible organism is the cause of the infection, and the use of maximum doses as early as possible in the course of the illness. The prescribing of sulphonamides as drugs of convenience when bacteriological diagnosis is lacking, or when antibiotics are clearly the drugs of choice, is a practice which is to be condemned.

*Preparations, Administration and Dosage.* Of the several thousand sulphonamides which have been prepared, only a relatively small number have been used in therapeutics and fewer still are in general use. They can be considered in two main groups: (a) those which are readily absorbed from the gut

and are used in systemic infections, and (b) those poorly absorbed from the alimentary canal and which are therefore used for their local action in the bowel. Local application of sulphonamides to wounds and to the skin is not recommended, but they are sometimes used in solution in the conjunctival sac.

*Sulphonamides for Systemic Use.* The older preparations sulphanilamide, sulphapyridine and sulphathiazole have been replaced by less toxic and more effective drugs. They are no longer included in the BP and require no further comment here. Reference is made in the section on therapeutics to the use of sulphapyridine in dermatitis herpetiformis. *Sulphadiazine* is 2-(*p*-aminobenzenesulphonamido)pyrimidine, a whitish, almost tasteless, crystalline powder insoluble in water and in the common organic solvents. *Sulphamerazine*, 2-(*p*-aminobenzenesulphonamido)-4-methylpyrimidine, resembles the former drug in its physical characters, and *Sulphadimidine* which is the 4:6-dimethylpyrimidine derivative is also similar. The *sodium* salts of these three pyrimidine derivatives are freely soluble in water forming highly alkaline solutions. *Sulphadimidine Sodium* is included in the BP. *Sulphafurazole* is 5-(*p*-aminobenzenesulphonamido)-3:4-dimethylisooxazole and *Sulphasomidine* which is 4-(*p*-aminobenzenesulphonamido)-2:6-dimethylpyrimidine, are newer preparations: they have been mainly employed in urinary tract infections. All these sulphonamides are dispensed as tablets for oral use each containing 0.5 G.; and a variety of flavoured suspensions for pædiatric use are also available. The sodium salts of the pyrimidine derivatives and the diethanolamine salt of sulphafurazole are available for intravenous injection.

*Administration and Dosage.* Sulphonamides are given by mouth, the tablets preferably being crushed and then swallowed with copious drinks of fluid. In adults with severe infections the initial dose should be 3 G. so that an adequate blood level may rapidly be attained. Thereafter therapy should be continued with 1-1.5 G. every 4-6 hours for 6-10 days depending upon the severity of the infection and the response to treatment. Therapy beyond 10 days is rarely called for, and the incidence of toxic effects rises as treatment is prolonged. Usually the drug may be



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discontinued 3 days after the temperature has fallen to normal levels. In all save the most severe infections 6-hourly dosage is adequate. Exceptionally in, for example, severe meningitic infection or when vomiting or coma prevents oral therapy, the drug may have to be given parenterally. For the purpose Sulphadimidine Sodium is recommended, given intravenously in a dose of 1-2 G. The Injection is dispensed in  $33\frac{1}{3}$  per cent solution and this should be diluted to 10-20 ml. in physiological saline before injection. Care should be taken to prevent leakage of sulphonamide solution around the vein as tissue damage amounting to ulceration and sloughing may occur; and the injection should not be repeated more often than 6-hourly. Oral therapy should be substituted as soon as the patient's condition allows. It is particularly important to secure a high urinary output when sulphonamides are given intravenously because of the increased risk of crystalluria, and sulphadimidine is preferred to sulphadiazine or sulphamerazine for the same reason. Sulphafurazole Diethanolamine may be given intravenously, but is only indicated if an adequate urinary output cannot be readily maintained. Intramuscular and subcutaneous administration of these preparations should be avoided and they must *not* be given intrathecally because of the risk of serious damage to the cord: this applies equally to patients suffering from meningitis, as excellent results are obtained by other routes of administration. In infections of the urinary tract a lower level of dosage is usually satisfactory because the drug is excreted in high concentration in the urine; 2 G. followed by 0.5-1 G. 6-hourly will usually suffice and treatment need not be given for more than 6 days.

In children (who tolerate sulphonamides well) the following scheme of doses may be recommended:

Up to 1 year	.	.	$\frac{1}{6}$	adult dose
1-3 years	.	.	$\frac{1}{3}$	" "
4-10 "	.	.	$\frac{1}{2}$	" "
11-15 "	.	.	$\frac{2}{3}$	" "

Further details concerning the choice of preparation and precautions to be observed during sulphonamide therapy are given in the section on therapeutic uses.

*Absorption, Fate and Excretion.* All the sulphonamides listed above are readily absorbed from the gastro-intestinal tract after oral administration, and some 70-90 per cent of the dose reaches the blood-stream. Although minor differences in the rate of absorption of the different compounds have been observed, this is not of practical importance. As is to be expected, the administration of the drug in suspension with a large draught of fluid when the stomach is empty results in more rapid absorption than when the tablets are swallowed whole after a meal; and if alkaline mixtures are given, this also hastens absorption but does not increase the total amount absorbed. Sulphonamides are poorly absorbed from the rectum and colon.

After a single dose peak blood levels are reached in about 4 hours, though there is considerable variation from one person to another. After therapeutic doses the levels of free drug are usually in the range 5-15 mg. per cent which is adequate to provide optimum bacteriostatic activity. After absorption sulphonamides circulate partly bound to the plasma albumin and partly in solution in the plasma. The protein-bound fraction is inactive as such, but the conjugation is loose, and the drug is released from albumin as excretion of sulphonamide proceeds. The amount bound varies from one compound to another, but is at least 50 per cent of the total drug in the plasma.

Sulphonamides are distributed throughout the body tissues and readily reach the cerebrospinal fluid and other body fluids.

The concentrations attained in the tissue fluids are lower than in the plasma, because only that fraction not bound to the plasma proteins is available for diffusion. For example, *sulphadiazine* reaches a concentration in the CSF of some 50-80 per cent of the simultaneously determined plasma level, whereas in the case of *sulphadimidine* the figure is 30-70 per cent. The difference is due to the greater degree of plasma-albumin binding of *sulphadimidine* compared with *sulphadiazine*. It is for this reason that *sulphadiazine* has often been considered the sulphonamide of choice in meningitis, but in practice adequate bacteriostatic levels of all the sulphonamides under consideration can easily be obtained in the CSF after oral administration.

The sulphonamides are altered in the body, especially in the

liver. Some oxidation products are formed, but the major change is acetylation at the para-amino grouping. The percentage of the total drug in the body changed in this way varies from about 15 per cent in the case of sulphadiazine and sulphasomidine to about 40 per cent in the case of sulphadimidine. This is mainly due to the fact that sulphadimidine is more slowly excreted than the other two compounds and there is therefore more time for acetylation to occur. The acetyl derivative has no antibacterial properties but retains the toxic properties of sulphonamides.

*Excretion.* Sulphonamides are eliminated from the body by the kidney, only negligible amounts being excreted in the faeces, sweat and other body secretions. Up to 90 per cent of the administered dose can be recovered in the urine and excretion is fairly rapid. In the case of sulphadiazine, sulphafurazole and sulphasomidine, about one-half of the amount given is excreted in 24 hours, and in 48–72 hours excretion is complete. Sulphadimidine and sulphamerazine are excreted more slowly and this warrants less frequent administration of these drugs to maintain adequate blood levels. The acetylated products are generally excreted more quickly than the free forms so that the amounts of the former in the urine tend to be higher in relation to the unchanged sulphonamide than is the case in the blood. Sulphasomidine, however, is exceptional in that the percentage of total drug found in the urine in the conjugated form is much the same as in the blood.

The concentrations of sulphonamide in the urine are 10–25 times greater than in the blood, a fact which accounts for their value in urinary infections and their tendency to be precipitated from the urine and to cause hæmaturia.

The importance of the varying solubilities of the acetylated and unchanged sulphonamides in relation to urinary pH and the precautions necessary to prevent crystalluria are mentioned below.

*Toxic Effects.* A large number of toxic reactions may occur when sulphonamides are used *therapeutically*—in contrast to the lack of pharmacological effects upon the tissues even if large

single doses are given. It should be stressed, however, that the modern drugs are much less likely to produce serious toxic reactions than the earlier compounds, and provided precautions are taken during treatment the overall incidence is now low.

*Urinary Tract.* The commonest complication of sulphonamide therapy is caused by crystallisation of the drug or its acetylated metabolite from the urine. Crystallisation occurs in the renal tubules and sedimentation takes place in the collecting tubules and calyces. This leads to renal irritation and sometimes colic and hæmaturia; in severe cases obstruction in the urinary tract and anuria may ensue. The various sulphonamides differ in their solubilities in acid and alkaline urine (p. 55). From this table it will be seen that in acid urine sulphadimidine, sulphafurazole and sulphasomidine are much more soluble than sulphadiazine and sulphamerazine, and this is confirmed by practical experience, as the former group of drugs rarely produces this complication. When sulphonamides are given it is essential that an adequate fluid intake be maintained—sufficient to ensure in adults a urinary output of at least 1,500 ml. in 24 hours. Further, if sulphadiazine or sulphamerazine is used the urine must be rendered alkaline with suitable doses of sodium bicarbonate and potassium citrate. Further details are given in Chapter 2 to which reference should be made.

As might be expected, serious complications of this type are most often seen in infants and young children treated at home, as in these circumstances it may be difficult to maintain an adequate urinary output. Sulphamerazine has acquired an unenviable reputation in this respect, and it is better avoided altogether in treating these patients.

A rare renal complication is the occurrence of acute tubular necrosis without demonstrable crystalluria. This leads to acute renal failure, and presents as severe oliguria or anuria but crystalluria is not present. The condition requires treatment designed to maintain fluid and electrolyte balance until the lesions have healed. Acute necrotising arteritis involving renal vessels occurs very rarely as part of the polyarteritis nodosa syndrome referred to below.

*Drug Fever.* Drug fever may occur with any of the systemic sulphonamides but is less common with the drugs now in use. The onset is usually between the 7th and 10th days of treatment and a skin eruption with pruritus is commonly present. Lymphadenopathy and arthritis are usually *absent* (cf. serum sickness). The fever is apparently due to sensitivity to the sulphonamides and is likely to recur if they are given on a subsequent occasion. In such cases the fever may appear within a few hours of administration of the drug. Treatment consists in withdrawal of the sulphonamide, when the temperature falls to normal within 72 hours. Drug fever must be distinguished from the fever due to the disease process for which the sulphonamide was given; and if the temperature does not fall to normal within a day or two after stopping the drug, some more serious condition—for example agranulocytosis—should be suspected.

*Skin Eruptions.* The incidence of skin rashes is about the same as that of drug fever and the two often occur together. A wide variety of morphological types may be seen including morbilliform, urticarial, nodose, eczematous and—more rarely—purpuric, eruptions. Severe bullous dermatitis and exfoliative conditions are of exceptional occurrence. The rash may be localised, but more often is generalised; and mucous membranes may also be involved. Conjunctivitis in particular is a common accompaniment. As noted above, fever and general malaise often accompany the rash and the blood may show eosinophilia. The application of sulphonamides to damaged skin is particularly liable to cause eczematous dermatitis, and in some patients exposure to sunlight tends to precipitate the lesions.

The onset of dermatitis is usually between the 7th and 12th days of treatment, but if the patient has received sulphonamides on a former occasion the rash may appear much earlier. Sulphonamide therapy should be stopped if skin lesions appear; and as sensitisation is long lasting, these drugs should be avoided in patients who have shown this type of intolerance.

*Hepatitis.* This serious complication is fortunately very rare. The onset is early during the course of treatment (usually about

the 3rd day), and the majority of patients in whom hepatitis has developed have shown sulphonamide intolerance on a previous occasion. The clinical features are those of acute toxic hepatitis, and fatal hepatic necrosis has been reported.

*Blood.* Blood dyscrasias have been reported with all the systemic sulphonamides, but the incidence is low. *Agranulocytosis* has occurred most frequently. It is a late complication—that is to say after sulphonamides have been given for at least 10 days. The clinical course and hæmatological features do not differ from those of agranulocytosis seen as a complication of other kinds of drug therapy. It calls for immediate cessation of treatment, and penicillin should be given until the blood picture has been restored to normal. Sulphonamides should not be used again in such patients. *Acute hæmolytic anæmia* is very rare. The onset is sudden *early* in the course of treatment; and all the features of severe hæmolysis are present. This complication was most often encountered with sulphanilamide, and children of negro stock were most often affected. The mortality rate was high despite withdrawal of the drug, blood transfusion, and giving copious fluids. A more chronic form of hæmolytic anæmia with *Heinz inclusion-bodies* in the peripheral blood occurs in some patients given sulphonamides over a long period of time. Nowadays it is most often seen when salicylazosulphapyridine is used in the treatment of ulcerative colitis (p. 510). *Aplastic anæmia*, and *thrombocytopenic purpura* occurring alone are rare complications of sulphonamide therapy.

*Polyarteritis Nodosa.* Widespread vascular lesions histologically resembling those of polyarteritis nodosa have been described in patients who have died from the complications mentioned above.

Apart from the urinary tract obstruction the other conditions listed are *hypersensitivity reactions*. It is believed that the basis of all these lesions is an antibody-antigen reaction, antigen formation resulting from the combination of sulphonamide with tissue protein. The fact that patients can be sensitised to sulphonamides in this way is a strong argument against the injudicious use of these drugs.

*Miscellaneous Toxic Effects.* The gastro-intestinal upsets include nausea and vomiting. These are rarely troublesome with the modern sulphonamides, but were so constant when sulphapyridine was used that adequate treatment was often impossible. Headache, vertigo, mental depression and somnolence are seen in some patients, especially if sulphonamides are administered to ambulant patients. All these effects are of central origin and do not usually interfere with continued therapy.

*Toxic psychosis* was by no means rare when sulphanilamide and sulphapyridine were used, and peripheral neuritis was likewise seen only with sulphonamides which are now obsolete, for example methylsulphathiazole. Cyanosis due to the formation of methæmoglobin or sulphæmoglobin was common with sulphanilamide and sulphapyridine but is not seen nowadays.

Systemic *acidosis* is produced by large doses of sulphanilamide, but not with the other sulphonamides under discussion. The mechanism is discussed on p. 36 in relation to acetazolamide.

#### THERAPEUTIC USES

Sulphonamides have a restricted field of usefulness because the numerous antibiotics now available are more efficient in many infections in which sulphonamides were formerly prescribed. Nonetheless they are still widely used and their cheapness and ease of administration contribute to their popularity, especially in domiciliary practice. These considerations of expediency should not, however, determine their use when other remedies are more appropriate; and the indiscriminate prescription of sulphonamides in the common self-limiting febrile illnesses, where bacteriological diagnosis is lacking, is to be deprecated.

Certain precautions during therapy are essential if the best results are to be obtained and untoward reactions reduced to a minimum. The drug should be given in adequate dosage for as long as may be necessary but no longer. It is seldom necessary to continue treatment for more than 7-10 days, and in urinary tract infections treatment for 6 days is usually adequate. Sensitisation reactions are uncommon with treatment lasting not more than one week. An adequate urinary output must be ensured (at least

1,500 ml. in 24 hours in an adult), and when this cannot be relied upon the use of another remedy should be considered. If sulphadiazine or sulphamerazine is used the urine should also be rendered alkaline. Infants and young children are especially liable to become dehydrated during acute febrile illnesses, and the possibility of crystalluria must be remembered in these circumstances. When treatment is prolonged beyond 10 days a careful watch for toxic effects should be kept, and ambulant patients should be instructed to report any untoward reactions such as sore throat, chills, or fever at once and to stop medication. If such precautions are taken the incidence of serious toxic effects is very low.

**CHOICE OF PREPARATION.** For many years sulphadimidine has been the drug of choice in this country. One important reason for this is the distinct therapeutic advantage—that the drug is soluble in an acid urine; another reason may well be the fact that the introduction of the drug was the outcome of British research and commercial enterprise. Sulphadiazine has been preferred in meningitis for theoretical reasons already mentioned, but in practice equally good results are obtained with sulphadimidine. If there is difficulty in maintaining an adequate urinary output sulphafurazole or sulphasomidine may be the preparations of choice. Sulphamerazine is probably best avoided.

*Urinary Tract Infections.* Sulphonamides are of great value in the treatment of uncomplicated infections of the urinary tract, particularly when *E. coli* is the causative organism. The management of a patient suffering from acute pyelonephritis may present a problem of some complexity. The diagnosis embraces clinical assessment, biochemical considerations (usually aspects of tissue dehydration) identification of the causal organism and its sensitiveness to chemotherapeutic agents *in vitro*, and so on. Such matters are considered in some detail in standard works on medicine and therapeutics. In general, however, as soon as the diagnosis has been made and a suitable specimen of urine obtained for examination, sulphonamide therapy (sulphadimidine) is started: the first dose is 2 G. and then 1 G. is given every 6 hours,



but the capacity of the kidney to concentrate the drug during its excretion warrants a reduction of the dose to 0.5 G. 6-hourly after 48 hours. Sulphonamide treatment should continue for 3 or 4 days after the acute symptoms have subsided: this usually entails a course of treatment lasting for a week. Long-term therapy with sulphonamides may also be of value in patients with chronic urinary tract infections, for example, pyelonephritis.

*Meningococcal Infections.* Sulphonamides are highly effective in the treatment of meningococcal meningitis and septicæmia. Full doses are employed and initial therapy should be by the intravenous route. Treatment should be continued for 9 or 10 days, as relapse may occur if the drug is discontinued earlier. Sulphonamides have also been used successfully in the prophylaxis of this infection in closed communities, for example in institutions and military establishments, during outbreaks of the disease. It has already been emphasised (p. 498) that neither meningitis nor any other disease justifies the injection of sulphonamides intrathecally.

*Influenzal Meningitis.* In meningitis due to *H. influenzae*, sulphonamides provide essential adjuvant therapy but should not be used alone. The best results are obtained if either streptomycin or chloramphenicol is used along with sulphonamides. In infections elsewhere due to this organism, for example acute exacerbations of pulmonary infection in patients with chronic bronchitis and emphysema, sulphonamides are not effective.

*Pneumococcal and Streptococcal Infections.* Although many strains of pneumococci and  $\beta$ -hæmolytic streptococci are sensitive to sulphonamides, penicillin is the drug of choice in these infections. In meningitis due to these organisms sulphonamides are often given as additional therapy, but it is doubtful if there is any advantage in using sulphonamides in this way. In rheumatic subjects, however, sulphadimidine in a daily dose of 1 G. is of proven value in the prevention of further attacks of rheumatic fever.

In a number of infections encountered abroad (or only rarely seen in Western Europe) sulphonamides are also employed combined with antibiotics. These include actinomycosis, cholera,

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plague, trachoma and lymphogranuloma venereum. Sensitive strains of *Shigella dysenteriae* are effectively treated with sulphonamides, and this is considered below.

Sulphapyridine is used in the treatment of dermatitis herpetiformis both to control the acute attack and to prevent recurrences in susceptible patients. For the latter purpose small doses of 1 G. daily may be given for prolonged periods. This benefit is independent of the bacteriostatic action of sulphapyridine, and other sulphonamides are not as effective as this drug. The action is not antagonised by PABA, and its pharmacological basis is not understood.

**SULPHONAMIDE MIXTURES.** Mixtures of sulphonamides were introduced to diminish the incidence of crystal deposition in the urinary tract. This is based upon the fact that several sulphonamides can be present in solution without affecting the solubility of each other. Thus a patient who is receiving substantial doses of a single sulphonamide may be in danger of developing crystalluria, whereas the hazard ceases to exist if the same urinary concentration of sulphonamide is achieved by the presence of several preparations of varying solubility. Further, it has been claimed that the lower concentration of individual sulphonamides in the tissues—when such mixtures are employed—decreases the likelihood of systemic toxic effects. It is doubtful, however, if these mixtures possess any advantages in these respects over, for example, sulphadimidine. Nevertheless such preparations are widely used. Those in common use in this country are Trisulphonamide Tablets, each 0.5 G. tablet containing sulphadiazine 185 mg., sulphathiazole 185 mg., and sulphamerazine 130 mg., and the Trisulphonamide Mixture for Infants. The latter preparation contains similar amounts of these drugs in each 4 ml. of flavoured suspension. Proprietary tablets and suspensions for paediatric use are also available commercially. The dosage employed is the same as for single “systemic” sulphonamides and they are used for the same conditions.

**SULPHONAMIDES FOR INTESTINAL CHEMOTHERAPY.** A number of sulphonamides are poorly absorbed from the gut so

that a high concentration of the drug is attained in the intestinal contents. The flora of micro-organisms in the bowel is thereby altered, and these preparations are used in the treatment of bacillary dysentery and to reduce the number of organisms in the gut before elective surgery on the colon.

*Sulphaguanidine.* This was the first compound to be used for intestinal chemotherapy, and was of great value in the treatment of bacillary dysentery during the early years of the Second World War. Chemically it is *para*-aminobenzenesulphonylguanidine monohydrate; it is a white crystalline powder, soluble to the extent of about 1:1,000 in water. The pharmacopœial dose is 10–20 G. in divided doses daily, and it is dispensed for use in 0.5 G. tablets. About 30 per cent of the ingested dose is absorbed from the bowel and this is metabolised in the usual manner. Toxic effects such as nausea, vomiting, fever and dermatitis are not uncommon, and renal complications also occur. For these reasons and because the drug is also one of the less potent sulphonamides it is seldom used nowadays.

*Succinylsulphathiazole.* This compound, 2-(*p*-succinylamino-benzenesulphonamido)thiazole is an insoluble white powder which has no bacteriostatic activity *in vitro*. It is available as official Tablets each containing 0.5 G., as a suspension containing 0.5 G. in 4 ml., and in various proprietary preparations. When taken by mouth less than 5 per cent of the ingested dose is absorbed from the intestine, and from the remainder sulphathiazole is slowly released into the bowel. This accounts for the activity of the drug *in vivo* even though it is inert *in vitro*. As sulphonamides are very poorly absorbed from the lower bowel, only traces of sulphathiazole appear in the blood but high concentrations are reached in the contents of the colon. Systemic toxic effects are virtually absent unless the patient has become sensitised to sulphonamide on a previous occasion. The adult dose is 10–20 G. daily in divided doses. Following administration of the drug the stools tend to become gelatinous in appearance, almost odourless, and number 3–4 daily. The number of bacteria in the stools is greatly reduced. Succinylsulphathiazole is used in the

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treatment of bacillary dysentery and prior to elective surgery of the bowel.

*Phthalylsulphathiazole* is an insoluble sulphathiazole derivative in which phthalic acid is substituted in the N<sub>4</sub> position. It is a white powder dispensed in 0.5 G. tablets. Its actions and uses are similar to those of succinylsulphathiazole, but as it is 2-4 times more active than the former drug the lower dosage schedule (10 G. daily) is usually adequate. It has less effect upon the consistence and appearance of the stools than has the succinyl derivative.

The sulphonamides used for intestinal infections may interfere with the synthesis of vitamins of the K and B groups by micro-organisms in the bowel, and this is more likely to give rise to symptoms if prolonged therapy is used. It is wise in these circumstances to give supplements of these vitamins. Liquid paraffin interferes with the action of these drugs by mechanically hindering their free admixture with the intestinal contents, and it should therefore not be used with this group of sulphonamides.

**TREATMENT OF BACILLARY DYSENTERY.** Sulphonamides have been used successfully in the treatment of this disease for many years. Either a poorly absorbed compound or a "systemic" sulphonamide may be used and there is little to choose between the results of treatment when either remedy is prescribed. The former have the advantage of avoiding systemic toxic effects, while the latter are claimed to eradicate the infection more quickly. In recent years a high proportion of strains of *Sh. sonnei*—which is the common infecting organism in this country—have become resistant to sulphonamides. For this reason many physicians prefer to use tetracycline to secure rapid bacteriological cure.

*Salicylazosulphapyridine.* This non-official sulphonamide is the *diazo* compound of *para*-aminosalicylic acid and sulphapyridine. It is a yellow powder, insoluble in water, and is marketed as tablets each containing 0.5 G. When taken by mouth the absorbed drug is deposited in connective tissue where its two com-

ponent parts are slowly released. The toxic effects are like those of sulphapyridine—nausea and vomiting, and a hæmolytic anæmia characterised by the appearance of Heinz bodies in the erythrocytes. Salicylazosulphapyridine is used exclusively in the treatment of chronic non-specific ulcerative colitis. The amount given daily is 4–6 G. in divided doses. An accurate assessment of the results of this treatment in ulcerative colitis cannot yet be made.

**SULPHONAMIDES FOR LOCAL USE.** The use of sulphonamides for wounds or skin lesions is not recommended because of relative inefficiency, a tendency to delayed healing, and a high incidence of allergic dermatitis. The following preparations are, however, used in the eye. (1) *Sulphacetamide Sodium*. This drug whose formula is shown in Appendix II has been used as a systemic sulphonamide in the treatment of urinary tract infections, but is now mainly used in inflammations of the conjunctival sac. It is prepared as buffered eye-drops in 10–30 per cent solution or as an Ointment containing 6 per cent of the drug. These preparations are used in the treatment of infections of the conjunctival sac and as prophylactic therapy after injuries to the eye. The stronger solutions cause considerable irritation, and prolonged use may lead to sensitisation dermatitis of the lids. (2) *The diethanolamine salt of sulphafurazole* is also employed as eye-drops containing the equivalent of 4 per cent of sulphafurazole, and a 4 per cent ointment is also available.

These preparations are used in the same way and have the same disadvantages as sodium sulphacetamide.

**NEWER SULPHONAMIDES.** In recent years a variety of new preparations have received clinical trials. The aim of the manufacturing chemist has been to secure high bacteriostatic activity along with favourable pharmacological properties including slow excretion, low acetylation, and high solubility in acid urine. These drugs, examples of which are *sulphamethizole* and *sulphamethoxyipyridazine* have not displaced the standard remedies: it is therefore unnecessary to give them further consideration here.

## ANTISEPTICS AND DISINFECTANTS

*Antiseptics* or bacteriostatic agents only arrest the growth of bacteria, whereas *disinfectants* or bactericides kill bacteria and may also kill their spores. Antiseptics which are also toxic to external parasites are called *parasitocides* or *ecto-parasitocides*. An antiseptic or disinfectant action may be produced by (a) *Physical means*—heat in various forms, ultra-violet light, X-rays, desiccation, etc., or (b) *Chemical agents*. The latter cannot be easily classified because, in many cases, their precise mode of action on bacteria is obscure. In the following pages a number of chemical compounds that have been used as disinfectants and antiseptics are grouped for convenience according to their principal chemical actions. Examples are given, but no attempt is made to provide a complete list. The rapid expansion of research in chemotherapy, and particularly the increasing knowledge of antibiotics, has made most of the older chemical antiseptics obsolete or obsolescent, viewed as therapeutic agents. Many of them retain importance in general hygiene because they can be used for disinfection of rooms, utensils, instruments, etc.

PHENOL AND RELATED COMPOUNDS. *Phenol* (carbolic acid) is of great historical interest: it was the disinfectant chosen by Lister. It is no longer used for this purpose; its place has been taken by many derivatives which are more effective and less toxic. Phenol itself acts by precipitation of protein, forming a loose complex with the protein—from which it readily escapes. It may, therefore, even in low concentration, penetrate deeply into tissues and cause extensive necrosis; this is usually painless as phenol has a marked local anæsthetic action. Although, therapeutically it is obsolete, phenol provides the standard against which the potency of other antiseptics is measured: their efficacy is expressed as a “phenolic” or “Rideal-Walker” coefficient. Phenol survives in daily use as an antipruritic agent in the symptomatic treatment of persistent itching in skin disorders (0.5 per cent in calamine lotion). It is occasionally used to destroy neural tissue: it can be injected into the sympathetic ganglia to

produce the effects of sympathectomy or into the spinal theca to destroy sensory nerve roots and so relieve intractable pain—a procedure which might be justifiable in a patient with painful and incurable carcinomatosis. It is also used as a sclerosant for injection into varicose veins.

*Toxic Effects.* Locally phenol is a caustic, and because of its ability to penetrate the skin it may produce extensive gangrene; this is particularly liable to occur if occlusive dressings are used. If ingested it produces acute gastro-enteritis. After absorption it has a depressant action on the central nervous system: large doses may result in coma. It is mostly excreted in the urine mainly as ethereal sulphates, but also as oxidation products (hydroquinone and pyrocatechin) which on further oxidation impart to the urine a dark colour—olive-green to brown—on standing (“carboluria”).

*The Cresols.* A soapy solution of *ortho*, *para* and *meta* cresols is widely used for disinfection of utensils, floors, and excreta. The toxic effects are fewer than with the phenols, though the mode of action is similar, as are the toxic effects when these occur. As they are incorporated in a soapy base they act as their own detergent. The cresols are obtained from tar distillates, and the preparation is cheap and moderately effective.

*Thymol*, though a fairly effective antiseptic, is only slightly soluble in water and finds its only use in mouth-washes and as a preservative. It loses much activity in the presence of protein; and it is an irritant on wounds and mucous membranes.

Various synthetic chlorinated phenolic derivatives are now available, and are probably the most satisfactory disinfectants.

*Chloroxylenol* in an alcoholic soapy base (for example in a solution of “Dettol”) is a widely used and relatively non-irritant antiseptic. Though its activity is reduced in the presence of blood or serum it retains significant bactericidal activity in these circumstances. It is much used in midwifery. *Chlorhexidine diacetate* (“Hibitane”) is a recently introduced antiseptic with a

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wide range of activity. It is non-irritant and can be applied to mucous membranes. Activity persists even in the presence of serum. It may be used for all purposes including the preparation of the skin for operation, and for this purpose it is dissolved in 70 per cent alcohol. *Hexachlorophane* is a non-irritant antiseptic. It is particularly effective against the Gram-positive cocci, and retains this activity in the presence of soap. It has therefore been incorporated into soaps for pre-operative preparation of the surgeon's hands.

**THE ALCOHOLS.** Alcohols (see also p. 180) possess an antiseptic action which is most marked in the higher aliphatic alcohols. The only one which is commonly employed is ethyl alcohol, at a concentration of 70 per cent *by weight*. Its antiseptic action is rather weak, and even this is dependent on using it as a 70 per cent solution; antiseptic activity falls off sharply if stronger or weaker solutions are used. It is commonly used to prepare the skin before venepuncture: the skin is gently swabbed and the alcohol allowed to evaporate.

**FORMALDEHYDE.** Formaldehyde is an effective disinfectant by virtue of its protein precipitant action; this action also accounts for its use as a fixative in preparing tissue specimens for histological examination. The fumes of formaldehyde are very irritant, and its use as a disinfectant is necessarily restricted to sterilisation of rooms and of some surgical instruments.

*Boric Acid* (Boracic Acid),  $H_3BO_3$ , is available as a white powder or in its crystalline state. It is sparingly soluble in water (1 in 25) but readily soluble in glycerin (1 in 4). It is a weak acid. *Sodium Borate* (Borax)  $Na_2B_4O_7 \cdot 10H_2O$ , has similar physical properties, but in solution it is faintly alkaline, and borax is even more soluble in glycerin (1 in 1). Boric acid is a weak antiseptic, but it is suitable for occasional application in solution to delicate mucous membranes. It should be emphasised, however, that (as with so many other drugs applied externally) repeated applications of boric acid or borates to one area of skin may cause a sensitisation reaction with the signs of inflammation. For general



surgical purposes it was at one time widely employed upon wounds, ulcers, etc., as a lotion (4 per cent), dusting powder, or in the form of boric acid lint and wool, either dry or as warm fomentations. Irrigation of body cavities, using solution of boric acid or borates, readily leads to toxic absorption. This use of boric acid is therefore no longer recommended—particularly as antiseptics are now available which, when employed in this way, are more potent and less toxic.

Taken *internally*, boric acid has little value as a gastric or intestinal antiseptic. It has been in use as a food preservative, but is now discontinued because frequent doses are apt to cause gastro-intestinal symptoms and constitutional upsets. The toxic effects of boric acid are partly attributable to the fact that the drug is excreted slowly by the kidney: it is therefore to be regarded as a cumulative poison. The lethal dose for an adult is about 20 G.

**THE HALOGENS.** Both chlorine and iodine are potent disinfectants. *Chlorine* is very powerful: a concentration of 0.1 part per million (ppm) is lethal to most micro-organisms within 30 seconds, but as it is a highly reactive substance it is very liable to be deviated from bacteria, and therefore it is of little value *in vivo*. Its main use is in water sterilisation, where heat sterilisation is not practicable. If little organic matter is present, a concentration of 0.5 ppm should be aimed at; if much organic matter is present chlorine is of little value. In the concentrations mentioned the taste of chlorine in the water is hardly noticeable. Calcium chloride and solutions of hypochlorite also possess a strong disinfectant action. Hypochlorite solution (Chlorinated Soda Solution) is used for irrigation of infected sloughing wounds; it contains approximately 0.5 per cent w/v of available chlorine.

*Iodine* in a 2 per cent solution in alcohol is used for the pre-operative sterilisation of the skin. In this organic solvent the penetration of iodine into the hair follicles and sweat glands is good; and this preparation is the most efficient skin sterilising agent available at the moment. Iodine kills most of the commonly occurring bacteria and also has a marked fungicidal action. It is

## ANTIBACTERIAL AGENTS

irritant and cannot be used on mucous surfaces. When a solution of iodine is applied to an abraded skin surface it causes severe stinging pain, but this is attributable to the effect of alcohol on exposed sensory nerve endings rather than to the presence of iodine. Local sensitisation reactions may occur.

Halogen substituted compounds, particularly with chlorine, are widely used, for example chloroxylenol (see above). These are effective against streptococci, but much less so against staphylococci. They are used principally as surface antiseptics and are remarkable for their lack of toxic action on normal tissues including mucous membranes.

**POTASSIUM PERMANGANATE.** Potassium permanganate is an oxidising agent—liberating nascent oxygen. It is a moderately potent antiseptic, effective against bacteria and fungi. It has also deodorant and mild astringent properties. Concentrated solutions are caustic; wounds should not be exposed to concentrations exceeding 1 in 5,000, but a 1 per cent solution may be applied to the intact skin and is useful in the treatment of mycotic infections. Dilute solutions of permanganate may be used as the lavage fluid in alkaloidal poisoning, the oxidising action producing destruction of the alkaloid. As solutions of salts of manganese are irritant, the fluid should be removed from the stomach when lavage is completed. Potassium permanganate, after contact with the tissues, undergoes reduction and the solutions returned are brown.

**HYDROGEN PEROXIDE** is an active oxidising agent and has antiseptic and deodorant properties. It is not a powerful antiseptic because the catalase of the tissues liberates its oxygen so rapidly that this has little time to have a lethal effect on the bacteria; but it inhibits the growth of anaerobic bacteria. The effervescence of the oxygen, however, detaches dead tissue and bacterial debris and thus cleanses the wound. Hydrogen peroxide is neither irritant nor toxic to the tissues and, as it is also a deodorant, it may be used either undiluted, or more usually diluted with 5–10 times its own volume of sterilised water, as an antiseptic for wounds, sinuses, burns, ulcers, etc., and to remove scabs in skin diseases. It also provides a means of removing

adherent dressings painlessly. It should be noted that there is a risk if hydrogen peroxide is syringed into cavities having a restricted egress; the oxygen evolved may cause embolism or spread the infection, for example in the ear. Hydrogen peroxide is a bleaching agent used to bleach hair. In the mouth, hydrogen peroxide, diluted with 10–20 volumes of water, is a cleansing antiseptic mouth-wash for stomatitis and gingivitis; it also bleaches the teeth but frequent use may soften the gums. For obvious reasons it is useless to give hydrogen peroxide to produce effects in the stomach.

THE HEAVY METALS (see also p. 579). The only heavy metal which has been widely used as an antiseptic is mercury, which is a widespread protoplasmic poison, acting by inhibition of sulphhydryl-containing enzyme systems. The action of mercury on bacteria is to produce reversible inhibition of bacterial activity rather than bacterial death. Protein greatly reduces the efficacy of mercurial antiseptics. Any compound containing mercury is potentially toxic, and therefore—except for its use in the dentist's amalgam—mercury is now little used. Ammoniated Mercury Ointment is mildly antiseptic and may be used in the treatment of staphylococcal infections of the skin; in threadworm infestation it is sometimes applied to the skin of the peri-anal region to diminish the migration of worms through the anal canal. Yellow Mercuric Oxide has been used as the antiseptic constituent of eye ointments ("golden ointment"). Mercuric chloride (Corrosive Sublimate) is soluble and is readily absorbed. Its use therefore exposes the patient to the hazard of toxic reactions. It should be regarded as an obsolete drug. Organic mercurial derivatives are available; they are usually less irritant and less toxic than the simple salts, but they are relatively poor antiseptics and probably do not merit therapeutic use.

ACTIVE CATIONIC SURFACE AGENTS (see also p. 608 (Soaps)). In solution these agents split into a complex large cationic molecule (possessing surface activity) and a small inactive anion. The surface-active cation possesses in addition a bactericidal action, but this is not invariably related quantitatively to the detergent action. The cation usually contains a nitrogen

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atom, often combined as a quaternary ammonium group to which long side-chains are attached. The most commonly used member of this group is *Cetrimide* (cetyl tetra-ammonium bromide). It is a colourless and odourless substance which is stable in solution. It is non-irritating and non-toxic, and it withstands boiling and autoclaving. Its activity is reduced in acid solution, but organic matter has little effect. Most of the common organisms of the skin are affected by cetrimide, but *Pseudomonas pyocyanea* is totally resistant to its action. Cetrimide is used on the intact skin and also for cleansing wounds and burns.

THE ACRIDINE DYE BACTERICIDES were used first as trypanocides (Ehrlich, 1912) but subsequently they were widely employed as bactericides. Their value as antiseptics depends on ionisation and the availability of the cation. It is thought that the acridines inhibit bacterial growth by interference with the respiratory enzymes of the organism. Various modifications have been made in the basic structure of the acridine compounds with conspicuous improvement in their bactericidal power. Many of these newer preparations would have received more detailed study under clinical conditions had it not been for the following circumstances: (1) the advent of antibiotics as therapeutic agents; (2) the occurrence of sensitisation effects following prolonged topical application of the acridine drugs.

The potentialities and the limitations of this group of antiseptics have emerged from the extensive use of Proflavine Hemisulphate. It is applied as a 1 in 1,000 solution in water or in normal saline. Proflavine has a relatively low toxicity for the tissue cells and leucocytes and its bactericidal powers are not diminished but are somewhat increased in the presence of serum and pus. This preparation was therefore widely employed in the treatment and in the prevention of pyogenic infection in wounds, burns, chronic ulcers, etc. In war-time it was used to impregnate dressings used as "first-aid" applications or protectives. Creams or emulsions, containing 0.1 per cent of proflavine and chlorocresol in a suitable ointment base can be used as an antiseptic application for small wounds. Proflavine is also contained in 'Triple Dye' (see below) formerly used in the treatment of burns.

## DILLING'S CLINICAL PHARMACOLOGY

**CRYSTAL VIOLET** (*Gentian Violet*) is an active antiseptic against Gram-positive organisms; it is not irritant to the skin or mucous membranes but has the disadvantage of its staining properties, which are greater on damaged than on healthy tissues.

For skin disinfection it is generally used along with Brilliant Green as a 0.5 or 1 per cent solution of each in water or 50 per cent alcohol, and chiefly in gynæcological practice where a non-irritant bactericide is essential. Aqueous solutions of Crystal Violet (1 per cent) alone are also employed as paints or applications for areas infected by boils or carbuncles and, in dermatology, for impetigo contagiosa, ringworm and infectious eczemas. *Triple Dye* is a solution of 2.29 G. each of Crystal Violet and Brilliant Green and 1.14 G. of Proflavine Hemisulphate in 1,000 ml. of water, and can be used as a first-aid antiseptic for burns.

Crystal Violet is also an anthelmintic for threadworm infestation (p. 570).

**BRILLIANT GREEN** is used as an antiseptic mainly in association with Crystal Violet; strengths of 0.05–0.2 per cent in water or normal saline are suitable. Ointments containing 1 or 2 per cent are applied on small wounds and on skin infections.

**DIBROMOPROPAMIDINE ISETHIONATE** is a dye-substance possessing activity against the pyogenic cocci and the common Gram-negative organisms. It is non-irritant and is used freely on skin and mucous membranes.

## BIOLOGICAL AGENTS

### INCLUDING IMMUNOLOGICAL AGENTS

Pharmacopœias include many standardised preparations which are used to combat illness arising from certain infectious diseases, or to protect the recipient in anticipation of his being exposed to these diseases. For example a patient suffering from clinical diphtheria derives benefit from prompt treatment with Diphtheria Antitoxin (p. 524). Had his susceptibility been determined earlier he could have been protected by means of Diphtheria Vaccine

(p. 523) which provokes in the tissues of the recipient the formation of antitoxin and a *protected state* summed up in the word Immunity. The main immunising agents included in the BP are mentioned in this chapter, but before listing them it is desirable to refer briefly to certain general principles.

In the present context *Immunity* can be defined as the state of resistance that exists to microbial infection. Immunity to the common infectious diseases is acquired naturally in one of two ways: it may be the consequence of suffering from the malady in its florid form—a *clinical* infection; or it may date from *subclinical* infection—occurring without perceptible constitutional upset or with minimal disturbances (“forme fruste”). These matters were understood by Chinese physicians at least 4,000 years ago. They applied immunological principles to the prevention of smallpox. A fragment of lint or thread soaked in the contents of a smallpox vesicle was applied to the nasal mucosa of the person requiring protection. A typical lesion developed at the site of inoculation, and the attendants hoped that it would remain well localised. Doubtless there was often moderate constitutional disturbance of a febrile type. These reactions sufficed to confer immunity. In the 18th century these methods were introduced into England and soon spread throughout Europe. They were abandoned, however, when it was proved that the relatively harmless lesions of cowpox conferred cross-immunity to smallpox. In general the deliberate use of virulent bacteria or of exotoxins as antigens is no longer practised. Such antigens are too dangerous for use in man. For clinical use there are preparations which are sufficiently attenuated to make them safe—without impairing their antigenic properties. When they are used as immunising agents, they act through the natural mechanisms used by the body in combating the disease itself; but the person actively immunised by artificial methods escapes the hazards of the overt infection and even those of the subclinical infection. It is obvious from the reference to the prevention of diphtheria that this type of immunisation is *ACTIVE*: it is the outcome of activity in the recipient’s tissues (mainly the reticulo-endothelial (RE) system). He is injected with an immunising agent which, on account of its chemical constitution, is *antigenic*—capable of exciting the formation of antibody.

Thus if the agent is a toxin (or a modified toxin called a *toxoid*) the antibody produced by the RE cells is an antitoxin. More than enough antitoxin is produced for immediate requirements. Further, the RE cells remain in a state of preparedness which enables them to flood the tissues with antitoxin if further provocation occurs in the shape of re-infection by the organism capable of producing this toxin. On the other hand if blood from an immune animal is removed and the serum is injected into a susceptible subject, the latter has obtained immunity *PASSIVELY*. This passive immunity is of short duration. Nevertheless it may be valuable as the only practicable method of protecting susceptible people newly exposed to infection; and there are circumstances in which the suppression of an incubating infectious disease may be a matter of the highest importance. Again the *therapeutic* use of antibody may be strongly indicated when it is clear that a patient is in the early stages of the disease in its manifest form.

The practice of *passive immunisation* is now relatively restricted. Immune sera are available for use in connection with the management of patients suffering from diphtheria, gas gangrene, tetanus, and scarlet fever complicated by toxæmia. There are many infectious diseases for which immune sera are not available; and in some of these specific therapy would seldom be worth while—for example in chicken pox and in rubella. There is a larger group of diseases which can be controlled—or even abolished—by prophylactic procedures which depend on *active immunisation*. They include diphtheria, whooping cough, tetanus, tuberculosis, poliomyelitis, yellow fever and smallpox.

The approach to immunisation is sometimes made easier by the use of *tests of susceptibility*—such as the Schick 't'cst. The applications of these methods have been useful in many ways. They have shown the duration of the immunity that an infant inherits from the mother as a result of transfer of antibodies across the placenta: such inherited immunity can be assumed to have disappeared by the time the infant is six months old.

Immune sera for therapeutic use could of course be obtained from human patients in convalescence. In general, however, it is much better to obtain such serum from horses which have been

made highly immune by inoculations of the antigen (for example diphtheria toxin) in graduated doses. When the serum has attained a suitably high titre, the horse is bled and the serum fractionated to make very concentrated preparations. There is strict supervision of every aspect of this work and official biological products must conform to the standards laid down in the BP. These products inevitably contain a certain amount of foreign protein (traces of horse serum). They are therefore liable to cause sensitisation phenomena: immediate reactions are anaphylactic in type (rare in man); late reactions (7-10 days after the injection) are those of "serum sickness" with the febrile state, a rash, enlargement of the lymph nodes, slight effusions into the joints (especially the knees and ankles) and pains in the limbs.

Vaccines and toxoids are used in the production of active immunity. Most vaccines are sterile suspensions, extracts or derivatives of bacteria, suitably prepared and standardised for clinical use. A few vaccines consist of living organisms artificially attenuated so that they are no longer pathogenic to man, though they retain their power to immunise: the vaccine of *Bacillus Calmette-Guérin* (BCG) is the outstanding example. Some diseases are attributable to the liberation of an exotoxin: the bacteria merely grow on the superficial tissues and do not invade deeply, but the toxin is absorbed and causes grave constitutional upsets (diphtheria, tetanus, gas-gangrene). It would be rational to use such toxins as antigens, but in practice they have proved to be too poisonous, and toxoids are used in human therapy. A toxoid is prepared by modifying a toxin—by chemical or other means: the toxoid becomes harmless to the recipient but retains its antigenic potency, that is to say, its capacity to excite the formation of antibody which is the specific antidote to the toxin. When vaccines or toxoids are used as prophylactics a series of three injections is usually given at appropriate intervals. Thus a mild response to the first injection is followed by a disproportionately vigorous response following the second and third doses. Any tendency for the state of immunity to diminish is conveniently countered by the occasional use of a "booster" dose—which results in a rapid rise in antibody level.

Immunisation is usually started after the passive immunity



inherited from the mother has declined. The child should be immunised against diphtheria, tetanus, pertussis and smallpox. Less frequently the immunisation programme includes other diseases such as tuberculosis and poliomyelitis. In order to reduce the number of injections required certain antigens have been combined. When this is done care must be taken that the dose of each is an adequate antigenic stimulus, or the response to a strong antigen might block any response to a weaker antigen. It is also necessary to be certain that no immunity exists to either antigen from previous infection or immunisation; should this be the case, the secondary response to the known antigen prevents completely the primary response to the unknown. Yet another difficulty about the use of combined antigens is that their use appears to increase the risk of the subsequent occurrence of paralytic poliomyelitis.

*Routes of Administration.* Antisera may be given intravenously, intramuscularly, or by deep subcutaneous injection. The intravenous route should be used as a matter of routine, and it is essential when an immediate high concentration is required. The object is to neutralise as much as possible of the available toxin in the body fluids before it becomes "fixed" in the tissues and no longer accessible. Vaccines are given by deep subcutaneous or intramuscular injection; the few exceptions to this will be dealt with individually.

*Toxic Reactions.* With antisera, reactions of all grades of severity from local allergic reactions to severe anaphylactic shock may occur. With the use of refined preparations the incidence of these reactions is considerably reduced. Anaphylaxis may occur even on the first injection of serum, particularly in subjects who have a history of allergic disorders. In these or in patients who have previously had serum, a trial dose of 0.1 ml. of serum should be given subcutaneously. If no general reaction occurs within half an hour then it is safe to give the full dose. Before intravenous administration of antisera, a full intramuscular dose should have been tolerated without reaction for at least 30 minutes. The injection should be made very slowly. Whenever

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serum is given adrenaline should be available, and a syringe should be ready to inject (subcutaneously) without delay should acute symptoms develop. Serum sickness may occur after a delay of about 7-10 days. Over the site of intramuscular injection of serum a large erythematous patch may appear with local itching for a few hours.

Vaccines and toxoids often produce local discomfort (pain and swelling), and may not infrequently produce a general reaction characterised by malaise, muscular aching and mild fever. These are usually transient and do not require special treatment. With vaccines containing attenuated living organisms, local reactions are of a different type and they will be discussed individually.

When certain combined immunising agents are used, or when the vaccines contain aluminium, there is a greater risk of paralytic poliomyelitis occurring in the injected limb. Hence vaccines of this type should not be used. The mechanism responsible for this effect is not clear.

The advent of sulphonamides and antibiotics has made many immunological products obsolete or obsolescent. In the following paragraphs reference is made to the therapeutic uses of a selection of biological products which are still employed in this country or elsewhere. In order to emphasise the importance of the preventive approach in this branch of medical practice, the preparations used for conferring *active immunity* are mentioned first.

### DIPHTHERIA

(a) ACTIVE IMMUNISATION. *Diphtheria Vaccine* is used. It is available as Formol Toxoid (FT), Alum Precipitated Toxoid (APT), Purified Toxoid, Aluminium Phosphate (PTAP), and Toxoid Antitoxin Floccules (TAF). The vaccine is injected intramuscularly.

The preparation commonly employed is FT. Infants receive the first dose of 1 ml. at the age of 9 months, and the second dose (1 ml.) is given not less than 4 weeks later. PTAP and APT are highly effective antigens, but as their use has been thought to increase the liability to poliomyelitis when this disease is epidemic, these preparations should be used only when the incidence of

poliomyelitis is low. For infants the dose is 0.5 ml. and this is repeated after not less than 4 weeks.

Adults are much more liable than infants and young children to show reactions to diphtheria antigens. TAF is the preparation of choice for immunising susceptible adults.

Susceptibility to diphtheria is determined by means of the Schick Test (see below). It is unnecessary to perform this test in the case of infants—all of whom over the age of 6 months may be regarded as susceptible to the disease. The test has revealed that 90-100 per cent of infants vaccinated against diphtheria become immune within six weeks of receiving the second dose of the prophylactic.

(b) PASSIVE IMMUNISATION. *Diphtheria Antitoxin* has a specific neutralising action on the exotoxin produced by *C. diphtheriae*. The antitoxin is obtained by immunising horses: the horse serum is suitably treated to yield a concentrated product, the essential fraction being "immune globulins". To give temporary protection to a child (thought to be susceptible to diphtheria and newly exposed to a patient suffering from the disease) a dose of 2,000 Units is injected intramuscularly. If in fact the child is incubating diphtheria, this dose of serum given on the first day effectively prevents the onset of symptoms because the infection is aborted. After 3 or 4 weeks the child should receive Diphtheria Vaccine to ensure the development of active immunity. If the patient is found to be suffering from the florid disease he must receive substantial doses of antitoxin. The dose needed can be assessed only by an experienced physician—who takes into account the severity and the duration of the disease. If clinical diphtheria is just beginning (first-day case) 24,000 Units should be injected; if it is a second-day case 48,000 Units are given; third-day and fourth-day cases with severe toxæmia established require 96,000 Units or more. A relatively small dose of antitoxin given *early* in the course of the disease is almost certain to lead to rapid defervescence; and even enormous doses do not compensate for delay in starting treatment. Diphtheria antitoxin given in the treatment of the florid disease should be injected *intravenously* unless there is good reason for avoiding this route.

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Treatment is begun promptly on a clinical assessment: several days may elapse before a bacteriological report is made on swabs sent for examination.

The value of this preparation is readily demonstrated by experimental methods carried out on laboratory animals. First, steps are taken to determine the Minimal Lethal Dose of a solution of diphtheria toxin when injected intravenously in a rabbit. Subsequently other animals of approximately the same weight are given *antitoxin* intravenously. It can be shown that when protected in this way the animal can receive doses of toxin greatly in excess of the MLD without showing any untoward effects. Experiments on these lines are also used for determining the potency of batches of antitoxic serum; that is to say the serum is assayed biologically and the antitoxin content is expressed in Units per ml.

Antibiotics (penicillin or erythromycin) are not effective in the treatment of diphtheria. The essential requirement is to combat the toxæmia: if this is done promptly and thoroughly the causative organism is disposed of by the natural defence mechanisms of the body tissues; or the bacteria may remain at the site of infection (the carrier state) and though harmless to the patient, may require to be eradicated by various measures—such as antibiotic therapy or removal of tonsils and adenoids.

## TETANUS

(a) ACTIVE IMMUNISATION. *Tetanus Vaccine* is used. This is a simple solution of tetanus toxoid. Alum-precipitated tetanus vaccine is also available but it is little used in Britain.

The usual scheme of dosage is: 0.5 ml.; after 6 weeks 1 ml.; and after 6-18 months 1 ml. Excellent results have been obtained from tetanus immunisation. The procedure is carried out routinely for soldiers, agricultural workers and others specially exposed to the risk of infection. Booster doses should be given every few years or when the circumstances increase the hazard of contracting tetanus.

(b) PASSIVE IMMUNISATION. *Tetanus Antitoxin* is used. This preparation neutralises the toxin produced by *Clostridium*

*tetani*. Its therapeutic applications, though more limited than those of the analogous preparations mentioned above, are nevertheless extremely important. If a patient has sustained a wound in circumstances which warrant the suspicion that it may have become infected with *Cl. tetani*, (for example in agricultural workers, battle casualties and in street accidents), a small dose of tetanus antitoxin 3,000 Units intramuscularly given *at once* virtually eliminates the danger to which the patient is exposed—that of developing florid tetanus in the period of a month or so following the injury. As a matter of routine, the patient should also be actively immunised. Appropriate surgical measures in dealing with the wound are of course justifiable in themselves but they also tend to reduce the risk of occurrence of tetanus.

If preventive measures against tetanus are omitted (or if they fail), the florid disease may develop, and *antitoxin is almost useless*—because the toxin is fixed in the tissues of the nervous system and cannot be neutralised. Clearly, therefore, it is impossible to exaggerate the importance of preventive measures in the therapeutic approach to tetanus. If symptoms of tetanus appear, massive doses (250,000 Units) should be given intravenously, but even these heroic doses contribute slightly if at all to the patient's chances of survival.

### WHOOPING COUGH

**ACTIVE IMMUNISATION.** Pertussis Vaccine is used. It is a sterile suspension of "Phase 1 *Bordetella pertussis* organisms having a potency at least 1.5 times that of the standard preparation". The potency of the organisms is determined by an intracerebral mouse-protection test.

Pertussis vaccine is used almost exclusively for the immunisation of children. The results are undoubtedly worth while but are not as striking as those obtained in diphtheria prophylaxis. Whooping cough is often a serious disease in infants—especially in those of poor physique—and if immunisation results only in diminishing the severity of the disease, it is fully justified as a life-saving measure. The first dose of 1 ml. is given when the infant is 3 months old, and two more doses are injected at intervals of 4 weeks. Booster doses (1 ml.) are recommended at the age of 12

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months and just before starting school at the age of 4 or 5 years.

Local reactions and slight constitutional upsets are not uncommon after pertussis vaccine. Rarely paralysis has occurred in the inoculated arm; and as a precaution pertussis vaccination is carried out only when the incidence of poliomyelitis is low.

Pertussis vaccine is considered worthless in the treatment of established whooping cough. There are no preparations for passive immunisation.

### SCARLET FEVER

(a) ACTIVE IMMUNISATION. Scarlet Fever Prophylactic is used: it is the toxin of *Streptococcus hæmolyticus*. Susceptibility to scarlet fever can be demonstrated by means of the Dick Test—which is the analogue of the Schick Test used for assessing immunity or susceptibility to diphtheria. By using the Dick Test it is easy to demonstrate the conversion of susceptibles to immunes after suitable courses of treatment with Scarlet Fever Prophylactic. The preparation is injected in graduated doses called Skin Test Doses (STD)—the unit of dosage being the amount of toxin that produces local erythema at the site of intradermal injection. Thus, the initial immunising dose is 500 STD, followed by 1,000, 5,000, and 15,000 at weekly intervals; a final dose of 25,000 STD is given 4 weeks later.

Immunity lasts for about twelve months and it is usually reserved for doctors and nurses working in scarlet fever wards. Local and constitutional reactions are not uncommon: they can be reduced in severity by injecting the preparation very superficially beneath the skin, and by adding to each injection 0.2 ml. of Adrenaline Injection.

(b) PASSIVE IMMUNISATION. *Scarlet Fever Antitoxin* neutralises the toxin produced by *Streptococcus pyogenes*. This is the toxin which has a selective action on blood vessels and causes intense vasodilatation and the characteristic rash (a diffuse and punctate erythema). The causative organism is easily attacked by means of penicillin or a sulphonamide and this therapeutic measure is now almost a routine procedure. The only specific remedy for the *toxæmia*, however, is the pharmaceutical prepara-

tion Scarlet Fever Antitoxin—which should be injected intravenously, when used therapeutically for its curative effect. Many physicians reserve antitoxin for patients who show signs of severe toxæmia. It is probably more logical to give a relatively small dose of antitoxin as a matter of routine (in addition to penicillin therapy) as soon as the disease is diagnosed, in the hope of preventing the disabilities of toxic scarlet fever; but while scarlet fever continues to be a mild infection most physicians regard this procedure as hardly justifiable.

The prophylactic and curative uses of Scarlet Fever Antitoxin (that is to confer temporary *passive* immunity) are analogous to the uses of diphtheria antitoxin. If a person is thought to be incubating scarlet fever the onset of the disease can be prevented by injecting 3,000 Units. Here again, however, current practice is to depend exclusively on penicillin therapy on the grounds that it suffices to attack the streptococcus. There is now a great deal of evidence in support of this view.

If scarlet fever is diagnosed and a decision is made to use antitoxin, 10,000–40,000 Units should be injected according to the physician's assessment of the severity of the toxæmia.

**MIXED GAS-GANGRENE ANTITOXIN.** This is a mixture of the antitoxins which neutralise toxins generated in the various types of gas-gangrene infection—*Cl. welchii*, *Cl. oedematiens* and *Cl. septicum*.

It is given to patients who have sustained wounds which are likely to be infected with the clostridia of gas-gangrene (battle casualties, street accidents, etc., with deep laceration of skin and muscle). Appropriate surgical attention to the wound is highly important in reducing the incidence of gas-gangrene and its severity. The use of antibiotics in preventing wound infection in general has reduced the occurrence of gas-gangrene as a supervening infection, but antibiotics and sulphonamides applied to wounds are of limited value in eradicating gas-gangrene organisms. Used prophylactically a dose of 10,000 Units is injected intravenously. If gas-gangrene is established, toxæmia is combated with large doses—90,000 Units of the mixed antitoxin. In such circumstances bacteriological diagnosis of the type of clostridial

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infection would be undertaken, and then the corresponding antitoxic serum would be used (called a monovalent serum) in preference to the mixed antitoxins (polyvalent serum). Separate antitoxins are available for patients known to be suffering from gas-gangrene caused by *Cl. œdematiens*, *Cl. septicum* and *Cl. welchii* respectively.

## TUBERCULOSIS

**ACTIVE IMMUNISATION.** A preparation of *Bacillus Calmette-Guérin* (BCG Vaccine) is used. This artificially attenuated strain of living bacilli is prepared under the most stringent conditions, and is accurately standardised for its content of living organisms. It must be used within ten days of preparation. When BCG vaccine is administered to tuberculin-negative subjects the conversion to positive reactors approximates to 100 per cent within two months. Associated with the positive reaction to tuberculin, immunity to tuberculosis seems to be conferred—particularly against the primary infection; and the incidence of active tuberculosis is reduced to approximately one-sixth. Nevertheless progressive post-primary type lesions can still occur in vaccinated subjects if the infecting dose is large enough.

In practice BCG vaccine should be given to infants and young children. It is essential that the children of parents with active tuberculosis be immunised, and similarly children and tuberculin-negative adults require immunisation if they have been in contact with a patient suffering from tuberculosis—that is to say with lesions which are potentially infective. Young adults especially, and those who have not previously been in contact with the tubercle bacillus should be tuberculin tested and, if negative reactors, be given BCG vaccine if there is any possibility that they might come into contact with the organism. The obvious example of people in this category is that of nurses and medical students.

The vaccine is administered intradermally by the multiple pressure method. Local and constitutional reactions are rare. The dose is 0.1 ml. which contains 0.05–0.1 mg. of living cells. Following vaccination a local erythematous papule at least 5 mm. in diameter should develop and persist for about ten weeks.



Measurement of this lesion should be carried out at 6 weeks, and if its diameter is less than 5 mm. tuberculin testing should be repeated. If the lesion is larger than 5 mm. in diameter vaccination should be regarded as successful. Rarely local ulceration occurs, and sometimes a primary complex is set up between the site of inoculation on the upper outer aspect of the arm, and its regional lymphatics. With properly prepared vaccine progressive local lesions and generalised tuberculosis are not found. There is a theoretical hazard in giving BCG vaccine to those who are already tuberculin-positive, in that they might develop a necrotic reaction at the site of inoculation. This in fact does not seem to occur, though a local lupoid lesion may be produced. Vaccination should not be carried out in the presence of active tuberculosis, though here again the potential dangers appear to have been exaggerated; sensitisation reactions only are reported. In those who are already tuberculin-positive, vaccination with BCG has no increased protection to offer and, because of the possible risks, it should not be carried out.

#### TYPHOID (ENTERIC) FEVER

**ACTIVE IMMUNISATION.** The preparation used is Typhoid-paratyphoid A and B Vaccine. Each ml. of the vaccine contains *Salmonella typhi* 1,000 million, *S. paratyphi A* 500 or 750 million, and *S. paratyphi B* 500 or 750 million.

The preparation gives immunity to about 70 per cent of those vaccinated, and protection lasts for about one year. It is widely used in the Armed Forces and by travellers in parts of the world where enteric fevers are endemic.

A course consists of a first dose of 0.5 ml. subcutaneously followed by a second dose of 1 ml. after 10 days. A local inflammatory reaction commonly occurs and within a few hours there is often a transient fever—sometimes accompanied by a rigor: the injections are therefore given in the late afternoon.

#### POLIOMYELITIS

**(a) ACTIVE IMMUNISATION.** The preparation used is Poliomyelitis Vaccine. It contains three types of poliomyelitis virus grown on monkey kidney tissue culture and inactivated by means

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of formaldehyde. In Britain the vaccine originally used was prepared from Type I strain of the Brunhilde (Enders) virus as it was considered to be less virulent than the Salk vaccine used in North America. Subsequently both preparations have been widely used in this country. The vaccine (1 ml.) is injected intramuscularly into the upper arm. The second dose is given 3-6 weeks later, and the third dose after an interval of not less than 7 months. It is desirable to avoid giving other vaccines (especially BCG, Yellow Fever, and Smallpox Vaccines) during the four weeks following administration of Poliomyelitis Vaccine.

Since the adoption of strict testing of poliomyelitis vaccines, accidents attributable to the inclusion of live virus have been eliminated. Constitutional upsets from the vaccine are rare—in relation to the enormous number of injections that have now been given. Protection is not absolute, but large-scale observations on children have shown that the introduction of vaccination has reduced the incidence of the disease by nearly 50 per cent. Further, if the disease does occur among those vaccinated, there is a distinct tendency towards the non-paralytic type of illness.

(b) PASSIVE IMMUNISATION. It is possible to confer a measure of protection against the development of paralytic poliomyelitis by means of Human Gamma Globulin Injection. The preparation is given intramuscularly and the dose is 0.31 ml./Kg. body weight. Immunity is established by the second week after administration, and it has disappeared some four weeks later.

## YELLOW FEVER

ACTIVE IMMUNISATION. The preparation used is Yellow Fever Vaccine. It is "an aqueous suspension of chick embryo containing living virus vaccine of yellow fever virus, strain 17D, which is virulent for mice but avirulent for man" (*The Extra Pharmacopœia*, Vol. 1). The "LD 50" dose of virus is determined by intracerebral injection into mice. A prophylactic dose for man is not less than five hundred LD 50 doses injected subcutaneously. Active immunity develops by the 10th day after inoculation and persists for about 6 years—when re-inoculation is necessary in endemic areas.

## SMALLPOX

**ACTIVE IMMUNISATION.** Smallpox Vaccine is the preparation used. The organism is the living virus of *cowpox*. The material used in preparing this vaccine is obtained either from lesions on the skin of healthy mammals (calves) or from membranes of inoculated chick embryos. Vaccine obtained from living mammals is called "calf lymph". The dose is 0.02 ml. introduced into the human skin by scarification or by pressure inoculation. The vaccine is dispensed in a capillary tube. The technique of vaccination is best acquired by practical instruction. In the scarification method the skin over the deltoid is washed with soap and water and dabbed dry. It is then swabbed with alcohol and this is allowed to evaporate completely. A drop of vaccine is expelled on to the skin. A needle is then used to make a scratch in the epidermis ( $\frac{1}{4}$  in. long) through the vaccine; care must be taken not to draw blood. When the vaccine has dried, the area is covered lightly with a sterile dressing. The skin must not be treated with antiseptics other than alcohol.

Primary vaccination is carried out in infancy—when the child is 4–6 months old. If primary vaccination is deferred until school age or adolescence, severe reactions are more likely to occur and there is some risk of post-vaccinal encephalitis—though this complication is a rarity.

The incubation period for smallpox is 14 days. Vaccination confers immunity in 12 days. Hence, vaccination within 24 hours of exposure to smallpox nearly always gives complete protection. When vaccination is carried out from the 2nd to the 4th day following exposure, some modification of the infection may be expected. After the 4th day vaccination has no effect on the course of the disease: a florid attack of smallpox is therefore likely to occur in the susceptible "contact".

## MIXED VACCINES

The growing practice of immunisation against various infectious diseases has resulted in a formidable programme of inoculations for infants in the first year of life. This imposes consider-

## ANTIBACTERIAL AGENTS

able discomfort and inconvenience on all concerned. Steps have therefore been taken to combine some of the standard methods of immunisation. The principle is important and of practical value, but also has its limitations. The antigens which have been combined include Diphtheria-Tetanus Prophylactic (BPC), Diphtheria, Tetanus and Pertussis Vaccine (BP), and Diphtheria and Pertussis Vaccine (BP). Poliomyelitis infection appears to be more common after the use of mixed vaccines which contain Pertussis Vaccine *and Alum* than after the use of vaccines which contain no alum. Other VACCINES which are listed in the BP or the BPC include:

*Cholera Vaccine* which contains killed cholera vibrios, is used prophylactically where the disease is endemic. Protection lasts for only about 6 months. Dose: 0.5 ml. followed by 1 ml. after 4 weeks, injected subcutaneously.

*Plague Vaccine.* This contains *Pasteurella pestis* killed with formaldehyde. The prophylactic dose is 0.5 ml. followed by 1 ml. after 2 weeks, injected subcutaneously. A boosting dose of 1 ml. should be given every 6 months in areas where the disease is endemic. Local and constitutional reactions are common but subside after a day or two.

*Rabies Vaccine* is a viral vaccine and consists of "killed or attenuated rabies fixed virus in an aqueous suspension of uncontaminated brain tissue derived from animals previously injected intracerebrally with fixed virus" (BPC). It is used for the protection of people who have been bitten by a rabid dog or other animal infected with rabies. Antirabic treatment given in these circumstances protects against the onset of hydrophobia. For details regarding the preparation of the vaccine and its mode of administration, reference should be made to the BPC and to works on general medicine.

*Typhus Vaccine* is a sterile suspension of killed *Typhus rickettsiæ*. Inoculation creates immunity to louse-borne and murine

typhus. The modern approach to prophylaxis, however, is to destroy body lice by means of Dicophane; and to treat sporadic cases of typhus by giving chloramphenicol or one of the tetracycline group of antibiotics—which provide a specific cure.

*Staphylococcus Toxoid* is used to create active immunity to staphylococcal infection where this is a recurring malady or a chronic condition not amenable to other therapeutic measures (for example recurring acne, boils, and in chronic staphylococcal osteomyelitis). Dose: 0.5 ml. of a 10 per cent solution is injected intramuscularly. Provided that the local and general reactions are not intolerable further doses are given at intervals of one week, the amount of toxoid being gradually increased until the patient is receiving 1 ml. of undiluted toxoid.

## HUMAN GAMMA GLOBULIN

**PASSIVE IMMUNISATION.** Protective antibodies against measles, rubella, poliomyelitis, and infectious hepatitis exist in the blood as gamma globulins—having developed as a result of clinical or sub-clinical infection with the micro-organisms of these diseases. These antibodies are available for therapeutic use as a 10 per cent solution for intramuscular administration as Human Gamma Globulin Injection; the preparation is made from human plasma by a process of fractionation. The introduction of Human Gamma Globulin as a method of protection by passive immunisation represents an important technical advance on the use of immune sera obtained from human convalescents. It has been employed in the following circumstances:

(a) *Measles*: to protect infants who are seriously ill or debilitated on account of other diseases and in whom contact with a known case of measles has created a serious hazard. *Dose*: Infants under 1 year receive 250 mg.; children aged 3 years or over receive 750 mg.

Attenuation of measles (as distinct from complete suppression) is often to be preferred because the disease—even in a modified form—confers immunity. The attenuating dose is 250 mg.

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(b) *Rubella* (German measles): to protect pregnant women who have not previously had this infectious disease. The danger of suffering an attack of rubella during the first 16 weeks of pregnancy lies in the fact that the disease greatly increases the risk of congenital abnormalities occurring in the fœtus.

(c) *Poliomyelitis*: To confer passive immunity on infants under 1 year, 500 mg.; and larger doses are given to older children—up to 1.5 G. for a child aged 7.

(d) *Infectious hepatitis*: the disease can be prevented by giving 250–500 mg. intramuscularly. Human Gamma Globulin is rarely used for this purpose because the susceptibility of an individual exposed to infection is difficult to estimate (in contrast for example to the situation that exists where young children have been exposed to measles).

Other protective sera which are listed in the BP or the BPC include:

*Anthrax Antiserum*. If used at the onset of the disease this antiserum is of therapeutic value. The dose is 40 ml. injected intravenously. The essential treatment, however, is to give a substantial dose of penicillin.

*Botulinum Antitoxin* neutralises the toxin of *Clostridium botulinum*. Its therapeutic value is open to doubt. Persons who are known to have eaten infected food should receive 50 ml. of the antiserum intravenously as a prophylactic. If botulism develops, this dose should be repeated every 12 hours.

*Dysentery Antiserum* (*Shiga*) contains antitoxin which neutralises the toxin produced by *Shigella shigæ*. It is a specific remedy, useless in other forms of dysentery. Further, it is employed only as a supplement to antimicrobial treatment with sulphonamides or antibiotics (chloramphenicol or tetracyclines). The dose is 100,000 Units every 12 hours intravenously.

*Leptospira Antiserum* may be used as a supplement to antibiotics in the treatment of *Leptospira icterohæmorrhagiæ* infections (Spirochætal jaundice); it is of no value in *Leptospira canicola* infections.

## DIAGNOSTIC AGENTS

A number of antigens are used as diagnostic agents. The more important ones are mentioned below. Technical details regarding their use are available in textbooks of infectious diseases and in *The Extra Pharmacopæia*, Vol. 1.

**SCHICK TEST TOXIN AND SCHICK CONTROL.** Schick test toxin is a sterile filtrate from a broth culture in which *C. diphtheriæ* has been grown. It contains the diphtheria toxin in an amount which is standardised by biological testing. On intradermal injection into a person without antibodies to diphtheria toxin, a patch of erythema is produced which lasts for several days and may be associated with epithelial desquamation. This is known as a *positive reaction* and the person showing it is described as "Schick-positive"—that is to say he has no antibodies to diphtheria toxin and is therefore susceptible to the disease. In such circumstances immunisation should be carried out. In the immune person, circulating antibody neutralises the injected toxin and no reaction should take place at the site of injection. Certain persons are susceptible to the ingredients of the culture medium and may produce an apparent positive reaction. A "control" is therefore essential; Schick Control is Schick Test Toxin which has been inactivated by heating to a stated temperature. If the reactions to the test toxin and the control are identical then the reaction is said to be a false positive or pseudo-reaction: this indicates immunity. The pseudo-reaction is usually more transient than the true positive reaction. If the reaction to test toxin is significantly greater than that of the control, then the reaction is positive and indicates susceptibility.

Both Schick Test Toxin and Schick Control are injected intradermally (commonly in the flexor aspect of the forearm) in a dose of 0.2 ml. Conventionally, the toxin is injected into the left forearm and the control into the right forearm.

**DICK TEST TOXIN and DICK TEST CONTROL** are official preparations used to test susceptibility to Scarlet Fever. The Toxin is "scarlet fever toxin (the sterile filtrate from a culture in

a suitable liquid medium of a toxigenic strain of *Streptococcus pyogenes*), or material obtained therefrom, diluted to make the mixture isotonic with blood and to ensure that 0.2 ml. contains a skin test dose" (BPC). The control is prepared by inactivating Dick Test Toxin solution: this is done by heating the preparation under stated conditions. The rationale for the test is identical with that which applies in the Schick Test. In practice, however, pseudo-reactions are so rare that the use of a control is unnecessary. Results are read at 24 hours and at 48 hours. A Dick-positive reactor is susceptible to Scarlet Fever; a Dick-negative reactor is immune. The dose of both preparations is 0.2 ml. by intracutaneous injection.

**TUBERCULIN PURIFIED PROTEIN DERIVATIVE.** This is a protein extract from a fluid culture medium in which *Mycotuberculosis* var. *hominis* has been grown and from which the organisms have been removed by filtration. It is supplied as a dry powder which is made up as an aqueous solution immediately before use. It is used as a diagnostic agent to demonstrate hypersensitivity to the tubercle bacillus or its products. This state of sensitivity is associated with previous tuberculous infection or BCG immunisation, and is often associated with some degree of resistance to tuberculous infection.

The preparation is available in strengths varying from 10 units of Tuberculin Purified Protein Derivative to 1,000 units in each ml., and 0.1 ml. is injected intradermally. The weakest should be used first. A positive reaction is indicated by the development of erythema and induration round the site of the injection. Should the reaction be negative, then each strength should be used in turn before the person is finally considered not to react to tuberculin. In contradistinction to the Dick and Schick tests, a positive reaction to tuberculin indicates hypersensitivity to the tubercle bacillus or its products and therefore indicates previous infection. If there are no signs of active tuberculosis a positive reaction may be taken to suggest some degree of immunity to tuberculosis. A negative reaction indicates susceptibility to infection.

The intradermal injection of tuberculin purified protein derivative is known as the *Mantoux test*. This test may be used



in diagnosis in children who have not been immunised with BCG; the presence of a positive reaction in a child suspected of having tuberculosis is regarded as strong evidence for this diagnosis. It is also used before BCG immunisation, other than in the newly born. Negative reactors, that is those susceptible to infection, are immunised. Positive reactors already possess the same degree of immunity that BCG confers, and therefore do not require immunisation.

## CHAPTER 16

# DRUGS USED IN SYPHILIS, PROTOZOAL INFECTIONS AND METAZOAL INFESTATIONS

### ANTILUETIC DRUGS

SYPHILIS is pre-eminently a preventible disease. The advent of antibiotics has provided the means of curing syphilis *in its early stages*. Penicillin has been shown to be highly effective in the treatment of syphilis. Given in sufficient dosage it can cure 97 per cent of sero-negative cases at the primary stage of infection. In many clinics penicillin is used to the exclusion of other specific remedies; in others a course of bismuth injections is given to guard against recurrence. Although organic arsenicals were formerly used as the drugs of choice in syphilis, they have been discarded almost universally.

Penicillin destroys the spirochæte of syphilis (*Treponema pallida*) *in vitro*. *In vivo* penicillin in aqueous solution is 10-20 times as effective as oxophenarsine in the treatment of syphilis in rabbits.

*Radical cure* means the complete eradication of the spirochæte from the body, and the term is necessarily restricted to the treatment of primary and secondary syphilis—when it is still possible for the tissues affected to revert to their normal state. This is not to be expected in tertiary syphilis: here the problems derive from irreversible changes in the tissues (for example, the central nervous system, large arteries, etc.) which are characteristic sequels to syphilitic infection. The kind of therapy required is decided after clinical and serological assessment of the individual patient. The data on which decisions are based will be found in textbooks of medicine. *Serological cure* means therapeutic success to the point of producing negative Wasserman and Kahn reactions.

## DILLING'S CLINICAL PHARMACOLOGY

**EARLY ACQUIRED SYPHILIS.** Any infection of less than three years' duration is treated with penicillin G. Long-acting preparations are preferred—such as benzathene penicillin G fortified with procaine penicillin G. Procaine penicillin G in oil containing 2 per cent aluminium monostearate can also be used. Various dose schedules are recommended. There is probably little to choose between them so long as a substantial quantity of penicillin is injected with minimum delay. One method is to give 2.4 million Units either at one visit or divided over two successive days. Other workers advise a total dose of 6 million Units: 600,000 Units twice weekly for 5 weeks as procaine penicillin G in oil containing the 2 per cent aluminium monostearate. A more comprehensive scheme takes into account the result of serological tests: (a) in early sero-negative syphilis procaine penicillin in aqueous solution is given, 600,000 Units daily for 10 days; (b) in early sero-positive syphilis the same dose is given for 20 days; (c) in late sero-positive syphilis (up to one year from the date of infection) the dose is 1 million Units daily for 20 days.

If the patient has had syphilis for more than 3 years, penicillin treatment, however vigorous, usually fails to produce any effect on the Wasserman or Kahn reactions. Nevertheless treatment is given in the hope of preventing the onset of signs of tertiary syphilis. The dose schedule mentioned in (c) above is suitable in these circumstances.

**LATE OR TERTIARY SYPHILIS** may involve the cardiovascular system or the nervous system (neurosyphilis). In cardiovascular syphilis, e.g. syphilitic aortitis with aortic regurgitation, 600,000 Units of procaine penicillin G in oil containing 2 per cent aluminium monostearate can be given twice a week for 5 weeks, and this can be repeated. Alternatively a single course can be followed by treatment with injections of bismuth, on the grounds that such patients should have the benefits of immediate anti-biotic therapy and the more sustained effects of bismuth therapy.

Neurosyphilis is treated in a similar manner with 600,000 Units of penicillin twice weekly for 5 weeks. In the syndrome called "general paralysis of the insane" many courses of treat-

## DRUGS USED IN SYPHILIS AND METAZOAL INFESTATIONS

ment are required with penicillin or with penicillin supplemented by courses of bismuth; such courses may be spread over a period of 1-3 years.

Phenoxymethylpenicillin given by mouth has a useful place in the treatment of congenital syphilis in children. It can also be used as a supplement to parenteral injections in neurosyphilis and in cardiovascular syphilis where a protracted course of therapy is indicated.

**THE JARISCH-HERXHEIMER REACTION.** This reaction sometimes called "therapeutic shock" occurs after the first treatment with penicillin or antisyphilitic arsenicals and in a milder form after bismuth injections. It is commoner after penicillin than after arsenicals, and this is consistent with the view that the reaction is attributable to sudden destruction of spirochaetes by the drug. Two responses are noted: there is a focal one in the nature of a flare-up of syphilitic lesions in the body, and a general one with fever and malaise. The reaction occurs in the first twenty-four hours of treatment. The focal reactions include swelling at the site of the chancre and enlargement of the neighbouring lymph nodes. If the reactions are mild, penicillin therapy need not be discontinued, but great caution is obviously indicated in such circumstances. In long-established syphilis the effects may be serious: for example the mouth of a coronary artery may become occluded from sudden swelling of adjacent syphilitic lesions; this might be fatal.

In patients with cardiovascular syphilis it has been suggested that therapy should start with injections of bismuth. The justification lies in making a less vigorous attack on the causal organism so that the risk of precipitating the Jarisch-Herxheimer reaction is reduced. Subsequently the patient can be given the benefit of intensive penicillin therapy. It is established that merely giving small doses of penicillin does not prevent Jarisch-Herxheimer reactions.

After penicillin injections there is nearly always slight pain and tenderness locally. General reactions include urticaria and generalised pruritus, but these are usually controlled easily by giving antihistamines (p. 284).

## ARSENIC

The trivalent organic arsenicals were formerly the most important drugs available for the treatment of syphilis and other spirochætal diseases. Their discovery by Ehrlich was undoubtedly an important landmark in the history of therapeutics, but the current view is that these drugs have been rendered obsolete by the introduction of antibiotics.

**NEOARSPHENAMINE** (sodium 3:3'-diamino-4:4'-dihydroxy-arsenobenzene-N-methylenesulphoxylate) is a stable compound, yellow in colour, and it dissolves in water to form a neutral solution which is suitable for intravenous injection. An initial dose of 0.3 G. is given dissolved in 10-20 ml. of water. The injections are repeated at weekly intervals for 10 weeks and the total amount given in such a course is 6 G. Several courses may be needed.

**SULPHIARSPHENAMINE** is disodium 3:3'-diamino-4:4'-dihydroxyarsenobenzene-N,N'-dimethylenebisulphite. This also is a yellow powder readily soluble in water. It has the advantage of being suitable for intramuscular injection. It resembles neoarsphenamine closely in its action and uses. The usual dose is 0.6 G.

**OXOPHENARSINE HYDROCHLORIDE** ("Mapharside") is the hemi-alcoholate of the hydrochloride of 3-amino-4-hydroxyphenylarsine oxide and contains 31 per cent of trivalent arsenic. It is a white hygroscopic powder and ampoules of oxophenarsine contain anhydrous sodium carbonate and anhydrous sucrose to render its solutions compatible and isotonic with human blood. The average single dose of oxophenarsine for adults is 1 mg. per Kg. body weight. The usual dose is 60 mg. dissolved in 10 ml. sterile water and given rapidly intravenously. The commencing dose of oxophenarsine is 40 mg. for a man and 20 mg. for a woman. This substance is well tolerated and is directly spirochæticidal. It is commonly given twice weekly for 10 weeks with injection of bismuth once or twice per week for the same period. Oxophenarsine is a preparation of constant composition—unlike neoarsphenamine which varies in composition and therefore in toxicity. Oxophenarsine is excreted completely in 2 days; neoarsphenamine is eliminated much more slowly. If R stands for a chemical radical, compounds of the type  $R-As=As-R$  like neoarsphenamine are oxidised in the

## DRUGS USED IN SYPHILIS AND METAZOAL INFESTATIONS

body to preparations with the formula  $R - As = O$  (e.g. oxophenarsine) before they act. These latter compounds react with the glutathione present in the tissues and in the organisms. The thiol ( $-SH$ ) groups in glutathione are attached to arsenic and the lethal effect on the bacteria is dependent on the inactivation of the essential  $-SH$  groups.

**DICHLOROPHENARSINE.** This substance is similar in action to oxophenarsine and contains two chlorine atoms attached to arsenic in place of oxygen. In solution it oxidises to oxophenarsine and this is the active agent.

*Toxic Effects.* When the solution leaks into the subcutaneous tissues there is always a local inflammatory reaction, and it may result in necrosis of skin and fascia. When organic arsenicals are given intravenously great care must therefore be taken to make sure that the end of the needle is lying in the lumen of the vein. Local pain in the arm may occur as a result of local spasm in the vein. Systemic reactions may occur at the beginning of treatment in the form of the Jarisch-Herxheimer reaction described above (p. 541). The most frequent complications from intravenous arsenical therapy are nausea, vomiting and diarrhoea. These symptoms are said to be prevented by abstinence from food for a few hours before treatment. Rarely "nitritoid crises" occur: the symptoms resemble those of shock, but they develop rapidly and may be followed by angioneurotic oedema. It is said that nitritoid crises never occur after oxophenarsine.

About 9 days after the initial injection of arsenicals in early syphilis a syndrome known as "Ninth-day Erythema" may appear. In many respects this is similar to serum sickness and consists of fever, erythema, and pains in the muscles and joints. It subsides spontaneously if arsenical therapy is discontinued. Exfoliative dermatitis may rarely occur. This is nearly always a serious complication: it begins as a mild pruritus early in the course of treatment and develops into severe dermatitis if arsenicals are continued. Trivalent organic arsenicals may also cause depression of bone marrow with thrombocytopenia, agranulocytosis or aplastic anaemia. Encephalopathy is a rare complication. As with other forms of parenteral therapy, faulty technique may result in the transfer of infection: homologous serum jaundice may thus be acquired.

Severe toxic reactions are treated by dimercaprol (p. 590).

## BISMUTH

Soluble bismuth salts are directly lethal to spirochætes *in vitro* but the same effect can be produced by solutions of oxophenarsine in one-tenth of the concentration. After treatment with organic arsenicals spirochætes disappear from the syphilitic chancre within a few hours; with bismuth the lesions take almost a week to become sterile. The gradual onset of the effect is of value in the treatment of late syphilis because it reduces the possibility of a Jarisch-Herxheimer reaction. As bismuth is not absorbed from the intestinal tract it is given intramuscularly in the treatment of syphilis and other constitutional infections by spirochætes.

Water-soluble preparations are absorbed rapidly and are liable to produce toxic effects. Also they are painful at the site of injection. Oily suspensions or suspensions in water of the finely divided metal are more slowly absorbed, less liable to produce toxic effects and are less painful at the site of injection. Most of the bismuth absorbed is eventually excreted in the urine.

When employed in the treatment of syphilis, bismuth is usually given once weekly as the Injection of Bismuth, 0.3 G., for a period of 10 weeks, the total dose being 3 G. This treatment is then suspended for a month to safeguard the patient against the risks of cumulation—consequent on the slow excretion of the bismuth. During this phase the bismuth stored in the tissues is gradually released into the bloodstream as soluble proteinates and excreted.

Bismuth is a valuable drug when given before penicillin in late syphilis and it does diminish the possibility of a Jarisch-Herxheimer reaction. It is of value also when the patient cannot tolerate penicillin.

*Toxic Effects.* These include pain and tenderness at the site of injection. With prolonged use discolouration of the gum margin develops as the metalloid is excreted by the buccal mucosa: a painful and offensive stomatitis may thus occur leading to toxæmia, anorexia and loss of weight. If the patient has nephritis or pyelonephritis, bismuth may increase the renal damage. Colitis and diarrhœa have been reported. Very rare complications are jaundice and dermatitis. It is recommended that before each injection the routine examination should include urine testing, examination of the mouth, and the patient's weight should be recorded. Stomatitis is much more likely to occur in the presence of pyorrhœa or other infective conditions of the buccal cavity.

## MERCURY

The use of mercury in the treatment of syphilis is now of historical interest only—but as such it is a topic which repays careful reading in older textbooks. Mercury in the form of Blue Ointment was given by inunction: some passed through the skin but much of it was volatilised and absorbed by inhalation. Therapy was “pushed” to the point of “salivating the patient”—deliberately producing early toxic effects as a proof of adequate dosage.

## IODIDES

Many clinicians believe that with the introduction of penicillin the use of iodides in the treatment of syphilis is obsolete. Others recommend that iodide therapy should precede by several weeks the beginning of injections of penicillin and bismuth in any form of late syphilis. Potassium iodide or sodium iodide are believed to hasten the resolution of gummatous lesions and are used in the treatment of cardiovascular or meningovascular syphilis and where gummata occur in any organ. The iodides are not curative and do not alter the Wasserman reaction; nor are the spirochaetes affected by iodides. The usual dose is 1–2 G. three times a day by mouth.

## LEISHMANIASIS AND SCHISTOSOMIASIS

## ANTIMONY

Certain preparations of antimony are of therapeutic value.

*General.* The inorganic salt potassium antimonyltartrate was once valued as an emetic (Tartar Emetic) and expectorant. Safer drugs have rendered obsolete these uses of tartar emetic, but it survives as a specific remedy for schistosomiasis and leishmaniasis—injected intravenously as a weak solution. As with other metals and metalloids used therapeutically, attempts have been made to reduce the toxicity of the essential constituent by the synthesis of organic preparations. Thus a number of relatively new compounds of antimony are available. In general they are to be preferred to tartar emetic, but there is no doubt that in the hands of skilled and experienced workers good results can be obtained from the use of inorganic antimonials.

Organic preparations of antimony may be pentavalent (Sodium Stibogluconate); or—like tartar emetic itself—they may be



trivalent (Stibophen and Sodium Antimonylgluconate). As might be expected, the trivalent organic compounds of antimony are more toxic than the pentavalent ones.

**PHARMACOLOGICAL ACTIONS.** When salts of antimony are directly applied to living tissues they produce local irritation. Thus when taken by mouth they result in nausea and vomiting; and if the bowel is affected diarrhoea is likely to occur. Similar harmful effects can be demonstrated on other tissues, but these phenomena are of interest to the toxicologist rather than the physician. In modern medical practice antimony is used only in the treatment of certain tropical diseases caused by protozoa. The antiprotozoal action of antimonials is attributed to their power to interfere with glucose metabolism in the parasite. In addition trivalent preparations of antimony inactivate sulphhydryl enzymes which are essential to the metabolism of trypanosomes. Antimony compounds are slowly absorbed from the gastro-intestinal tract. These drugs cannot be given orally because absorption is erratic and adequate doses cause severe intestinal irritation. They are therefore injected parenterally, and when potassium or sodium antimonyltartrate are used for their systemic effects they are given only by the intravenous route.

**THERAPEUTIC USES.** In leishmaniasis the pentavalent antimonials are the most useful and of these Ethylstibamine is the drug of choice. The initial dose is 0.2 G. given intravenously. If there are no untoward effects, doses of 0.3 G. are injected on alternate days until a total quantity of 5 G. has been administered.

For the treatment of schistosomiasis potassium antimonyltartrate (tartar emetic) or stibophen are used. Although tartar emetic is almost certainly more effective it is also more toxic. Tartar emetic should be freshly made up in sterile normal saline (0.5 per cent solution). An initial dose of 30 mg. is given slowly intravenously with the patient fasting and lying down. This dose is gradually increased every second day until a maximum single dose of 0.12 G. is being given; one course consists of a total dosage of 2 G. Stibophen is given in a total dose of 90 ml. of 6.3 per cent solution. The first three doses are 1.5 ml., 3.5 ml. and 5 ml.

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administered intramuscularly on successive days. Thereafter 5 ml. is given by the same route every second day until completion of the course.

In the treatment of filariasis, ethylstibamine and lithium antimony thiomalate (anthiomaline) are effective, though piperazine (p. 569) is being used widely in filarial infestations.

Stibophen and tartar emetic are effective in the treatment of lymphogranuloma inguinale. Stibophen is also given as in schistosomiasis, but the maximum dose of 5 ml. is given twice weekly only until symptoms and signs of the disease have been brought under control: the patient then receives a weekly injection of 5 ml. for the next 6 months as a precaution against relapse.

In mycosis fungoides, tartar emetic given intravenously in 1 per cent solution is sometimes of value. The first dose is 2.5 ml., the second 3.5 ml., and thereafter the full dose of 5 ml. is given on alternate days.

*Toxic Effects.* The symptoms of acute and chronic antimony poisoning resemble those caused by arsenic. With trivalent compounds—and especially after tartar emetic—severe coughing and sometimes vomiting may develop about half a minute after the intravenous injection. When preparations of the metals and metalloids are used therapeutically, toxic effects usually declare themselves towards the end of a prolonged course of treatment. Such drugs are often cumulative (p. 17) and disturbances are likely to occur in those viscera which are concerned with the metabolism or excretion of the chemical substance. Symptoms can sometimes be related to a selective effect on specialised tissues, and these particular cells may be specially vulnerable because the drug—in “toxic” concentrations—happens to interfere with one or more metabolic processes which are indispensable to normal cellular function.

After a prolonged course of treatment with antimony, pains in the joints and muscles are fairly common. Bradycardia often develops at this stage of treatment. “Pneumonia” is also reported as an occasional complication.

## MALARIA

INTRODUCTION. Many drugs are now available for use in malaria. Apart from cinchona and its chief alkaloid quinine, there are synthetic preparations. Their value has been assessed in human patients and—adopting experimental methods—in birds and mammals. Although a drug may be classed as a powerful antimalarial, it does not follow that the parasite is vulnerable at every stage of its life cycle. On the contrary, the lethal action of the drug may be restricted to one phase; and in other phases the plasmodium may be relatively or completely insusceptible to the toxic effect of the drug. Hence the potential value of an anti-malarial and the most effective way in which to use it clinically emerge only when its mode of action has been defined as precisely as possible.

But in areas where malaria is endemic, drug treatment for the individual patient suffering from the disease in its florid form is only one aspect of a complex problem. There is an extensive literature on the subject. Some idea of the limitations of chemotherapy can be obtained from the following brief statements:

1. Relief of the patient's symptoms is not invariably synonymous with radical cure.
2. The existence of infected mosquitoes is a potential menace to man and certain other mammals and to some birds; "reservoirs of infection" are readily created.
3. The social services must be organised to wage war relentlessly on the mosquito in all its breeding places. This policy is accepted because of the economic consequences of malaria.
4. If all the members of a community regularly take a suppressive drug *clinical* malaria can be abolished; but there are nearly always a few defaulters.
5. Prolonged use of a prophylactic drug may lead to the appearance of strains of plasmodium which are *resistant* to the action of the drug.
6. The human host, untreated or inadequately treated, survives by developing a degree of immunity to the infection. Thus man survives: so also does the parasite.

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In the following paragraphs the antimalarial drugs are mentioned individually and are briefly discussed. As a preface, however, the main points are summarised to show the mode of action and the potentialities of each drug:

	<i>Drug</i>	<i>Phase of Life Cycle Affected</i>	<i>Therapeutic Applications</i>
A	Quinine Mepacrine Chloroquine Amodiaquine	Only erythrocytic forms of malaria parasite	<i>In acute malaria</i> , they abolish symptoms but do not cure. Parasites elsewhere (e.g. in liver) are unaffected
B	Proguanil Pyrimethamine	(a) Erythrocytic forms (b) Exo-erythrocytic forms (e.g. in liver)	Prophylactic drugs: they prevent parasite from becoming established in RBC or in viscera
C	Pamaquin Primaquine	(a) Exo-erythrocytic forms (e.g. in liver) (b) Gametocytes	Complementary to group A: e.g. Chloroquine followed by course of Primaquine makes attack on parasite comprehensive N.B. Drugs which kill gametocytes protect health of <i>community</i>

## THE ANTIMALARIAL DRUGS

The prevention and cure of malaria will always be regarded as one of the classics of the history of medicine. The discoveries of Laveran (1845) and other medical scientists who followed him laid the foundations of modern practice in the treatment of malaria. The organism which causes this disease is a protozoon—a plasmodium—and its three common types produce characteristic clinical syndromes. Benign tertian malaria results from infection by *Plasmodium vivax* and has a serious tendency to relapse; *Plasmodium falciparum* produces malignant or subtertian malaria—often a severe illness with symptoms that are protean; and

infection with *Plasmodium malariae* causes the relatively rare form of quartan malaria.

Drug therapy in malaria cannot be profitably discussed without a brief reference to the life cycle of the malarial parasite. The parasite is injected into the blood of man by the bite of an infected female anopheline mosquito. The injected parasites (*sporozoites*) begin an asexual cycle in the human blood stream. After about half an hour, the sporozoites have disappeared from the peripheral blood: they can be found in the host's liver cells. During this exo-erythrocytic stage the parasites are appropriately called *cryptozoites*. The affected liver cells then rupture and the parasites, now called *trophozoites*, are set free. Some invade previously uninfected liver cells while others enter red blood cells where they grow as (i) sexual and (ii) asexual forms. In the asexual phase the nuclear chromatin material of the trophozoite divides (schizogony): this is the *schizont* stage. The schizont grows, distending the red cell envelope: eventually this ruptures, freeing numerous small bodies which are called *merozoites*. These merozoites do not remain long in the plasma: each one enters a fresh red cell. The other group of trophozoites disintegrate to release sexual forms, namely male and female *gametocytes*. These sexual forms can complete their further development only in the body of an anopheline mosquito. The transfer occurs when a mosquito bites an infected human being, and infected blood enters the mosquito's body. The continued development of the sexual phase occurs by the union of the male and female gametocytes in the lumen of the insect's stomach. Following this union, a *zygote* is formed which perforates the mosquito's stomach wall and produces a *sporocyst*. This sporocyst finally ruptures into the body cavity of the mosquito liberating *sporozoites*. These find their way to the salivary glands of the mosquito. Thus, the next person who is bitten by the insect is almost certain to receive an injection of sporozoites, and the life cycle of the malaria parasite is complete.

The periodic fever—which is typical of the classic type of malarial infection in man—signals the release of asexual merozoites into his bloodstream. As long as these asexual cycles are repeated the patient suffers from acute malaria. When conditions in the human host become unfavourable to the parasite, the

sexual forms or *gametocytes* are produced in greater numbers. In this form the parasite causes no symptoms in man. He is still infected, but suffers no disability of an acute kind: the disease has assumed a chronic form. At this stage the human subject enjoys a measure of immunity: he has some resistance to the parasites which prevents their rapid asexual multiplication in his tissues. Nevertheless he still harbours the gametocytes, and is therefore a reservoir of infection on which anopheline mosquitoes can draw. He is therefore accurately described as a *carrier*; and he creates a potential menace to the health of the community until the gametocytes have been eliminated from his tissues.

*Prophylaxis of Malaria.* A completely effective prophylactic agent is one which kills sporozoites or cryptozoites (the exo-erythrocytic stage) thus preventing an infection from becoming established in the human host. Such a prophylactic agent is not yet available. The physician therefore resorts to *suppressive treatment*. This simply inhibits the development of sporozoites (in the erythrocytic phase); rupture of the red cells is thus prevented and consequently the patient does not suffer from the "malaria" which is recognisable as a febrile illness. So long as the suppressive action is efficiently maintained there are no symptoms, but if it is suddenly discontinued, the characteristic clinical syndrome may recur.

## QUININE

Quinine is an alkaloid obtained from the bark of the cinchona tree which is a native of Peru and other parts of South America. The crude preparation known as Peruvian bark was first used in Western Europe as a remedy for malarial fevers in the early part of the 17th century; but it is clear that in South America, people had been familiar with the therapeutic value of the bark from much earlier times. The alkaloidal salts are now preferred—the sulphate (which is insoluble in water) and the bisulphate, hydrochloride and bihydrochloride, which are all soluble. The chief interest of quinine lies in its action on the malaria parasite. Other actions of quinine which are of less practical importance will be mentioned briefly.

The alkaloid is a general protoplasmic poison: it depresses many enzymatic processes, interferes with phagocytosis and inhibits growth of fibroblasts in tissue cultures. It is particularly toxic to leucocytes and protozoa but less so to bacteria. When applied to raw surfaces or injected, the soluble salts in solutions stronger than 0.25 per cent are at first irritant; paralysis of sensory fibrils then occurs resulting in prolonged local anæsthesia. If solutions of quinine salts are injected hypodermically or intramuscularly, local damage to the tissues may occur—sometimes amounting to necrosis.

A solution of quinine hydrochloride, 5-10 per cent. (with urethane, 3-6 per cent. to increase the solubility of the quinine salt) is injected in amounts of 0.5-5 ml. into varicose veins to cause sclerosis by irritation of the endothelium; similar injections can be used to sclerose hæmorrhoids, the solution being injected alongside the vein—not into the lumen of the vessel.

Quinine salts are intensely bitter and are therefore normally given in sugar-coated tablets. On the other hand, if these salts are being used as "bitters"—deliberately to produce a bitter taste and thus promote appetite—suitable preparations containing a trace of quinine are available. Given in large doses quinine may cause mild gastric irritation and nausea. In the upper intestine the alkaloid is readily absorbed. In order to produce the constitutional effects of quinine a soluble preparation should be prescribed.

The bisulphate and the hydrochloride are quickly absorbed from the small intestine and these are to be preferred. The sulphate should not be given as pills or tablets. The sulphate is a reliable preparation only when dispensed in solution with a weak mineral acid; and the tablets and pills of quinine sulphate should not be used because absorption is erratic. For practical purposes, it is therefore best to use preparations other than the sulphate.

*Antimalarial Action.* Quinine is not a complete prophylactic agent. Even when the human tissues are heavily loaded with quinine, they still permit the survival of the malaria parasite injected into the blood by infected anopheline mosquitoes. The drug certainly makes some impact on the life cycle of the plasmodium, and insofar as this results in freedom from symptoms,

quinine has great importance in clinical practice. It is schizonticidal; but it is not lethal to sporozoites, nor does it kill the exo-erythrocytic forms. The gametocytes of *P. vivax* and *P. malariae* are killed by quinine, but the sexual forms of *P. falciparum* are resistant. As a prophylactic suppressive drug a daily dose of 0.6 G. should be started the day before entering an infected area and continued for a month after leaving.

When malaria is diagnosed clinically—usually as an illness with fever and other signs—quinine should be given by mouth. In treating “benign” infections, one of the preparations—Quinine Hydrochloride, Dihydrochloride, Bisulphate or the Sulphate in acid solution—is given in doses of 0.6 G. thrice daily for a week. Then a dose of 0.6 G. daily should be maintained for 2 or 3 months. In malignant tertian infection 0.6 G. every 4 hours may be necessary until all symptoms and pyrexia abate. If a patient has serious symptoms such as excessive drowsiness, confusion or delirium, the drug should be given by intravenous injection: 0.6 G. of Quinine Dihydrochloride, dissolved in 20 ml. of Injection of Sodium Chloride, should be given *very slowly*. This method of treatment is not dangerous if rapid injection is avoided. Fully 3 minutes should be allowed for intravenous administration. If quinine is given too quickly there is a risk of inducing a sudden fall of blood pressure. The patient may also suffer from acute *cinchonism*. Many patients whose condition warrants intravenous medication with quinine are dehydrated. They therefore receive physiological saline by intravenous drip: a dose of quinine can be conveniently added to the first bottle of saline—usually given in the course of 1 hour. Intravenous therapy is of course merely a supplement to the routine of oral administration. Physicians who have no experience in the use of quinine by intravenous injection naturally prefer to give mepacrine intramuscularly.

Both as a suppressive agent and in the treatment of florid malaria, quinine is less effective than mepacrine and much less so than chloroquine. In therapeutic doses quinine has only minor effects on the central nervous system: it is a mild analgesic and a weak antipyretic. The effect of quinine on heart muscle is similar to that of its isomer quinidine, but when quinine is used in the treatment of malaria in otherwise healthy people, the effect of the



drug on the myocardium is rarely of clinical significance. Thus moderate doses of quinine have little effect on the normal heart or blood pressure in man. Grossly excessive doses of quinine cause vasodilatation by a direct action on the smooth muscle of the vessel wall. Flushing of the skin seen in quinine poisoning is attributable to peripheral vasodilatation; this action and direct depression of the myocardium account for the low blood pressure.

Quinine has an action on the gravid uterus. Once labour has begun quinine can intensify weak uterine contractions. In toxic doses it may cause abortion.

Quinine increases the tension response of skeletal muscle to a single maximum stimulus delivered directly to the muscle or through the nerve. It also increases the refractory period of muscle so that response to tetanic stimulation is diminished. The excitability of the motor end-plate is decreased and thus responses to repetitive nerve stimulation and to acetylcholine are reduced. Quinine increases the muscular weakness of patients with myasthenia gravis and improves the symptoms of myotonia congenita. Following the administration of quinine the alkaloid is mainly metabolised in the body so that less than 5 per cent is excreted unaltered in the urine: under ordinary conditions, cumulation does not occur.

Poisoning by quinine is due to overdosage or idiosyncrasy. When full doses are given at short intervals a group of symptoms occurs termed "cinchonism". Similar effects are sometimes caused by salicylates and cinchophen. In its milder form, the syndrome consists of ringing in the ears leading to deafness, headache, nausea and impairment of vision. With larger doses vertigo, deafness, contraction of the visual field, diarrhoea, abdominal pain and rashes of papular or urticarial character may occur. Headache, vomiting, delirium with depressed respiration, cold cyanotic skin, low blood pressure, extreme weakness, coma and death from respiratory arrest are noted in the severe forms of poisoning. The retina is seen to be pale from spasm of retinal arteries. Renal damage and acute hæmolytic anæmia occur on occasion. If there is idiosyncrasy to quinine, even a trace of the drug may produce obvious cinchonism. Quinine should be avoided in people known to have an idiosyncrasy, in patients

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with optic neuritis, and during pregnancy—especially near full term. In patients with auricular fibrillation it is important to bear in mind that the effects on the heart may be indistinguishable from those produced by quinidine (p. 300).

Preparations of quinine are still widely used in malaria, but the demand for synthetic drugs is steadily increasing—mainly because they are at least as effective as quinine and in general produce fewer troublesome complications. Quinine is now rarely prescribed as an analgesic and antipyretic but is employed occasionally as an oxytocic to initiate labour. Many popular bitter tonics taken with or without alcoholic beverages contain a slight trace of quinine in the form of a soluble salt. Quinine relieves the spasms of myotonia congenita and may be given as the bihydrochloride (0.3–0.6 G.) two or three times per day. It is sometimes effective in cases of myotonia atrophica. In a suspected case of myasthenia gravis quinine may be used in a “diagnostic test”. The dose is 0.6 G. orally repeated at 2-hourly intervals for 3 doses if necessary: muscular weakness is increased, but the effects are reversed when neostigmine is given. In a severe case this diagnostic test is unnecessary, and the intensification of paralysis in such circumstances might result in great distress.

## MEPACRINE

Mepacrine is 2-chloro-5-(4-diethylamino-1-methylbutyl-amino)-7-methoxyacridine. The dihydrochloride is commonly used and is a bright yellow crystalline powder sparingly soluble in water. It is available in 50 mg. or 100 mg. tablets. Mepacrine Methanesulphonate is a soluble salt available for intramuscular injection in a dose of 0.1–0.3 G. Mepacrine is readily absorbed from the alimentary tract and also quickly reaches the circulation after intramuscular injection. In the body, it is found mainly in the liver, spleen, lungs and adrenal glands; it is eliminated slowly. A high concentration is found in leucocytes, and mepacrine passes through the placenta and reaches the fœtus. It is found in the saliva and in lower concentrations in the plasma. The daily administration of mepacrine for about a week colours the skin yellow and this lasts for 2–3 weeks after stopping treatment.

Mepacrine does not stain the sclera of the eye; the pigment is therefore readily distinguishable from that of jaundice.

*Antimalarial Action.* Mepacrine is more potent than quinine, and the patient tolerates it more readily. It acts mainly on the erythrocytic phase, destroying the asexual erythrocytic trophozoites in all types of malaria. It is especially superior to quinine in the treatment of malaria caused by *P. falciparum*; and as the exo-erythrocytic forms of *P. falciparum* do not persist, this infection can be eradicated by a suitable course of treatment with mepacrine. *P. vivax* infections cannot be eradicated although acute attacks can be controlled. Mepacrine is a valuable suppressive drug and can be taken daily for an indefinite period (a year or more) without harm. If the person has been infected by *P. vivax* this infection will become apparent when the mepacrine is discontinued. The dose advised for suppressive therapy in adults is 0.1 G. daily. Treatment begins 2 weeks before entering the endemic zone and is continued for 1 month after leaving. After malaria suppression with mepacrine, relapses do occur due to *P. vivax*, but suppressive doses may be curative in falciparum malaria. Although mepacrine, as already stated, is more effective and less toxic than quinine, it is inferior to chloroquine as regards potency and toxicity. In the acute attack of malaria the usual dose of Mepacrine Hydrochloride is 0.2 G. every 6 hours for 5 doses and then 0.1 G. 3 times daily for 6 days. In addition to pigmentation of the skin, mepacrine occasionally causes side-effects and these include nausea, vomiting, headache, diarrhoea and insomnia. Rarely it produces a toxic psychosis. Various types of dermatitis have been described including a lichenoid variety.

Mepacrine has been used in a dose of 0.1 G. three times daily for 6 days in the treatment of *Giardia lamblia* infestation. Many physicians regard it as the drug of choice as an anthelmintic in tapeworm (*Tænia saginata*) infestation. Selected patients with chronic discoid lupus erythematosus and the acute disseminated form of the disease have been treated with mepacrine.

## CHLOROQUINE

Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutyl-amino)quinoline. The phosphate is the compound commonly used: it is a white, bitter, soluble crystalline powder, available in 0.25 G. tablets. Like mepacrine, chloroquine is readily absorbed from the alimentary tract. It is found in higher concentration in liver, spleen, kidney and lung. It is excreted slowly but the rate of excretion depends partly on the pH of the urine: if acid, the rate is accelerated; if alkaline, excretion is slower.

*Antimalarial Action.* Chloroquine has no action on the exo-erythrocytic stage of the plasmodium. It kills the erythrocytic forms of *P. vivax* and *P. falciparum*. It completely cures malignant tertian malaria (falciparum), and although it does not prevent relapses in benign tertian it prolongs the intervals between relapses. It is also an active suppressive agent and is superior to quinine and mepacrine in suppressing benign tertian (vivax) malaria. It need only be given once weekly as a suppressive agent in a dose of 0.5 G. Chloroquine Phosphate. It controls quickly the acute attacks of falciparum malaria and as a rule completely cures the disease. Also the acute attacks of vivax malaria are rapidly controlled and relapses are not so numerous. For the treatment of an acute attack 1 G. is given orally followed by 0.5 G. 6 hours later and a single dose of 0.5 G. on each of three successive days. Freedom from relapses can then be ensured by giving 0.5 G. once weekly. Chloroquine is less toxic than mepacrine, but slight headache, itching and gastro-intestinal complaints occasionally occur. Prolonged administration may cause a lichenoid skin eruption, but the lesions subside rapidly when the drug is stopped.

Chloroquine has been used in giardiasis and in lupus erythematosus (both the disseminated and the chronic discoid forms). As this drug is a powerful amœbicide and is found in high concentration in the liver, it has been used with success in hepatic amœbiasis (p. 566).

## PROGUANIL

Proguanil is  $N^1$ -*p*-chlorophenyl- $N^5$ -isopropyldiguanide and the hydrochloride is the salt commonly used. It is a white, crystalline, bitter-tasting powder sparingly soluble in water. Proguanil is slowly but well absorbed from the gastro-intestinal tract. The drug accumulates to a slight degree in the body, chiefly in kidney and liver and is rapidly eliminated when administration ceases. About 40–60 per cent of the oral dose is excreted in the urine, about 10 per cent in the fæces, and the remainder is metabolised.

*Antimalarial Action.* Proguanil kills certain strains of the exo-erythrocytic forms of falciparum infections and is also active against asexual forms of all species. It does not kill gametocytes, but it does inhibit the formation of the sporocyst in the mosquito and thus renders the mosquito non-infectious. (Transfer of the drug from man to mosquito occurs when the insect aspirates human blood while biting.) Proguanil is therefore a complete prophylactic for certain strains of falciparum malaria and can be used as a suppressive agent for the other types of malaria, although for this latter use it has no advantage over mepacrine or chloroquine. The prophylactic dose of Proguanil Hydrochloride is 100 mg. by mouth daily. Certain indigenous strains of parasites develop a high degree of drug resistance to proguanil.

As a therapeutic agent in the acute attacks of malaria proguanil alone, except in the susceptible strains of *Plasmodium falciparum*, is not satisfactory. A high relapse rate occurs and combined proguanil and mepacrine therapy gives better results. The dose is 300 mg. once daily for 10 days. Side-effects are rare but anorexia, vomiting and headache have been reported after prolonged administration. If the drug is taken after food, gastric upset is less likely to occur.

## AMODIAQUINE

This is one of the 4-aminoquinoline series. It adequately controls the acute clinical attacks of vivax or falciparum malaria. The drug is used as the dihydrochloride dihydrate ("Camoquin"),

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a light-yellow, water-soluble powder; it is dispensed as a tablet. When taken by mouth it is rapidly absorbed from the small intestine and is most highly concentrated in the spleen and liver. About 5 per cent of the ingested drug is excreted in the urine; the rest is metabolised. Transient nausea and vomiting, headache, diarrhoea and very rarely staining of the skin are among the side-effects recorded. This preparation has been given to pregnant women, and to patients with nephritis and with cirrhosis, and no ill-effects have been observed. The gametocytes and schizonts of vivax malaria are killed by this drug. It is also rapidly lethal to the schizont of falciparum malaria but acts very slowly on the gametocytes. It is a very powerful malarial suppressive and a weekly dose of 0.4-0.6 G. is effective. One single dose of 10 mg./Kg. can control the acute attack of vivax malaria. It is also of use in the treatment of amœbic hepatitis and in acute and discoid lupus erythematosus. Very large doses can cause leucopenia.

### PYRIMETHAMINE ("Daraprim")

Pyrimethamine is 2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine and in low dosage is an effective suppressive agent against *P. vivax* and may also kill the gametocytes of *P. vivax* and *P. falciparum*. Pyrimethamine is a tasteless white powder insoluble in water. It is dispensed as a Tablet containing 25 mg. The suppressive dose is 25 mg. once weekly. The acute attack of malaria is treated by giving 50 mg. on the first day followed by 25 mg. daily for 2 days. Large doses may cause megaloblastic anaemia.

### PAMAQUIN

Pamaquin is a synthetic substance and is an 8-aminoquinoline. It is an orange-yellow, insoluble powder with a bitter taste. After oral administration pamaquin is rapidly and completely absorbed from the intestinal tract, and the concentration in plasma reaches a maximum in 2 hours. This drug rapidly disappears from the blood stream into the tissues: less than 1 per cent is excreted in the urine and the rest is rapidly metabolised. When a patient receives pamaquin and mepacrine simultaneously, the concen-

tration of pamaquin in the plasma is much increased and its metabolic degradation is retarded. In these circumstances pamaquin often produces toxic effects. Hence in clinical practice these two drugs are not used at the same time: pamaquin therapy begins when the course of treatment with quinine or mepacrine has been completed (see below).

*Antimalarial Actions.* Pamaquin prevents relapses in vivax malaria. It kills the exo-erythrocytic forms of *P. vivax* and *P. falciparum* and it acts on the asexual forms of *P. vivax* and *P. malariae*. Its limited actions make it unsuitable for use as a prophylactic. The main effect of pamaquin is the destruction of gametocytes. If this can be achieved, the patient ceases to be a reservoir of infection: he no longer conveys malaria parasites to mosquitoes when they bite him. Thus, although pamaquin treatment is of no direct benefit to the patient convalescing from malaria, its importance to the community where malaria is endemic can hardly be exaggerated.

Pamaquin is a toxic substance. Therapeutic doses may cause anorexia, nausea, vomiting, muscular weakness and cyanosis. Rarely acute hæmolytic anæmia has been reported. The usual dose is 20 mg. orally three times per day for 5 days following a course of quinine or mepacrine.

The introduction of pamaquin was an important landmark in the history of malaria. It has served to emphasise once again that the "cure" of malaria presents complex problems: it involves much more than abolishing the discomforts of a febrile illness or even preventing their appearance in people exposed to infection. The treatment of malaria embraces all measures which interfere with the life-cycle of the malaria parasite in its asexual and its sexual phases. The role played by pamaquin has been mentioned. Other compounds, superior to pamaquin, are now available and some of these are described below.

#### PRIMAQUINE

Primaquine, an 8-aminoquinoline, is usually given as the phosphate: Tablets containing 7.5 mg. (base) are available. In the treatment of malaria the usual practice is to give chloroquine

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for the first 3 days followed by primaquine 15 mg. for 14 days. Primaquine is used in this way to produce radical cure in relapsing vivax malaria. It is a much less toxic drug than pamaquin: slight abdominal pain, mild anæmia, and cyanosis due to methæmoglobinæmia have been reported as side-effects. If the primaquine is taken after food or with an antacid the abdominal pain rarely occurs. The standard course of treatment—3 days on chloroquine followed by 14 days on primaquine—is generally regarded as the most effective treatment for infections caused by *P. vivax* and by *P. falciparum*.

## DRUGS USED IN THE TREATMENT OF AMŒBIC DYSENTERY (AMŒBICIDAL DRUGS)

INTRODUCTION. Amœbic dysentery is caused by the *Entamœba histolytica*—so called because this amœba has a destructive effect on the tissues of the host, especially on the colon. Infection occurs when a patient swallows material contaminated with these organisms in their encysted form: the cysts are digested in the small intestine and the young amœbæ are released. In the large bowel the young amœbæ become motile, multiply and invade the mucosa of the intestine. Erosion and ulceration are the characteristic lesions, and the clinical syndrome of dysentery develops accompanied by diarrhœa with blood and mucus in the stools. Many patients experience only transient symptoms, but they harbour the organisms in the encysted form and are then called “carriers”. If *Entamœba histolytica* migrates from the bowel to the liver by the veins and lymphatics it may cause “amœbic hepatitis” and this, if untreated, may pass to the stage of abscess formation. Again, amœbiasis may result in a state of chronic inflammation in the bowel wall. The outcome may be the formation of a localised mass of granulation tissue infiltrating the bowel wall: this is called an amœboma.

EMETINE. Emetine is an alkaloid obtained from ipecacuanha. It is prescribed as a soluble salt—the hydrochloride—for intramuscular injection in amœbiasis. The name of this alkaloid indicates that if it is taken by mouth it causes vomiting; the emetic



action of ipecacuanha is attributable to the emetine it contains. In the bowel, emetine continues to act as an irritant and causes diarrhœa. The practical importance of these statements lies in the fact that the oral use of emetine (or the hydrochloride) in the treatment of amœbiasis is not practicable, but the alkaloid can be conveyed to the diseased tissues in the blood stream by means of parenteral injection.

Intramuscular injection is the method of choice: subcutaneous administration causes painful swellings; and intravenous injection is both unnecessary and highly dangerous because the drug in high concentration in the blood stream may seriously depress the heart muscle. Emetine is excreted mainly by the kidney but so slowly that cumulation occurs: excessive doses or prolonged administration may also cause damage to the myocardium, and peripheral neuritis is an occasional complication. Emetine is a specific poison for *Entamœba histolytica*: it kills the motile forms but is much less effective against the cysts.

*Side-effects.* With therapeutic doses, side-effects are mild. Local reactions to the injections are not troublesome if the drug is injected deeply into a muscle. Nausea, vomiting and diarrhœa may be induced by emetine. Patients sometimes complain of tiredness and weakness while on emetine. The risk of toxic depression of the myocardium warrants the practice of keeping patients in bed during emetine treatment and for a week after the course of injections. Emetine should not be used if there is evidence of cardiac or renal disease; and in elderly or emaciated people care is necessary. It is a wise precaution to chart blood pressure readings daily during emetine treatment. A falling blood pressure and a rising pulse rate suggest myocardial damage.

*Courses of Treatment.* Emetine Hydrochloride is given intramuscularly and the dose is 60 mg. daily for not more than 10 days. Emetine is remarkably effective: it causes the acute symptoms of amœbic dysentery to disappear in 2 or 3 days, and there is a rapid reversion of the tissues to their normal condition. A course of emetine should not be repeated until an interval of at least 6 weeks has elapsed. Although emetine is a specific remedy in acute

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amœbiasis, it does not clear the bowel of cysts. The use of emetine alone, therefore, tends to increase the number of asymptomatic carriers. In amœbic hepatitis and in the treatment of granulomata and abscesses in other sites, emetine is strikingly effective.

EMETINE BISMUTH IODIDE (EBI). The advantage of this preparation is that it can be given orally: the emetine is released slowly in the alimentary canal, but the compound itself is a powerful amœbicide *in vivo*. It is a reddish-orange, insoluble powder with a bitter taste. The usual dose is 0.2 G. given in a gelatin capsule after the evening meal for 12 consecutive days. As with emetine therapy, the patient should be confined to bed and should remain there for a few days after treatment. Some physicians give a course of EBI following the use of 5-10 injections of emetine hydrochloride. This regimen is intended to eradicate cystic forms of the parasites: it is effective, but few patients can tolerate it because of nausea, colic and diarrhœa. For this reason EBI is used less frequently, its place having been taken by new synthetic substances such as those mentioned below.

CHINIOFON ("Yatren"). This is a mixture of 4 parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and 1 part of sodium bicarbonate. It is a light-yellow powder which has a bitter-sweet taste. Chiniofon is effective against motile and cyst forms of the entamœba but is of no value in amœbic abscess or hepatitis. This substance is poorly absorbed and the bulk of the chiniofon taken by mouth is excreted in the fœces. The drug therefore acts largely within the intestinal tract. An enteric-coated tablet (0.25 G.) is available and 0.75-1 G. is given by mouth three times per day for 10 days. Retention enemas are also used, especially in severe or resistant cases: 6 G. in 200 ml. of water (temperature not exceeding 44° C.) is given by rectum; the foot of the bed is raised and the enema is retained as long as possible. A daily enema may be given for 10 days. Oral chiniofon is not advised while enemas are being used. A notable side-effect is profuse diarrhœa which usually subsides after 2-3 days. Massive doses used experimentally have produced liver damage: the drug is therefore best avoided in patients suffering from hepatic disease. Chiniofon

should not be given to patients who have an idiosyncrasy to iodine. In ordinary circumstances it offers a safe and effective treatment in cases of acute and chronic amœbiasis.

**IODOCHLORHYDROXYQUINOLINE** ("Vioform"). This is 5-chloro-7-iodo-8-hydroxyquinoline and is a brownish-yellow insoluble powder with an iodine content of approximately 40 per cent. It is an amœbicidal drug effective against vegetative and cyst forms, but as the drug is poorly absorbed its amœbicidal action is restricted almost entirely to the bowel. The dose is 0.25 G. given in enteric-coated tablets 3 or 4 times per day for 10 days. A rest period of 10 days is then allowed before the course is repeated. In the 10-day interval Carbarsone may be given (see below). Side-effects from iodochlorhydroxyquinoline are rare: they resemble those seen after chiniofon; and likewise the drug should be avoided if there is hepatic disease or iodine idiosyncrasy. Clinically iodochlorhydroxyquinoline is used in amœbiasis only when the infection is intestinal. The drug, in tablet form, can also be used in the local treatment of trichomonas infections of the genital tract.

**DI-IODOHYDROXYQUINOLINE** ("Diodoquin"). This compound (5:7-di-iodo-8-hydroxyquinoline) is a tasteless, yellowish-brown powder almost insoluble in water and containing 52 per cent of iodine. The tablet in common use contains 0.65 G., and the total daily dose recommended is 30 mg. per Kg. of body weight for 15-20 days. A rest period of 2-3 weeks is necessary, but during this time Carbarsone may be given. This drug is of value only in the intestinal form of amœbiasis: it is active against vegetative and cyst forms. As it is a poorly absorbed substance constitutional upsets are correspondingly rare. Dermatitis, generalised furunculosis, pruritus and diarrhœa have been described as side-effects. This substance has also been used in lambliais resistant to mepacrine. Applied locally it is of value in vaginitis caused by *Trichomonas vaginalis*.

**CARBARSONE.** This is an organic pentavalent arsenical *p*-carbamino-phenylarsonic acid; it is an odourless, white powder insoluble in water, but it dissolves if the water is made alkaline.

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Tablets containing 0.25 G. are available. Carbarsone is amœbicidal because it contains arsenic which combines with the thiol groups in enzyme systems of the amœba. It is a less toxic drug than acetarsol. It kills vegetative amœbæ more slowly than does emetine, and it has no effect on amœbic abscess of the liver or on amœbomata elsewhere. When it is taken by mouth carbarsone is rapidly absorbed, but it is excreted only slowly in the urine. It is given orally in 0.25 G. doses twice daily for 10 days. Each course may be repeated several times but a rest period of 10 days should be given between courses because the slow excretion of carbarsone favours cumulation. It is an advantage that during treatment with this drug rest in bed is not necessary. Carbarsone can be given rectally as a retention enema (200 ml. of 1 per cent carbarsone in 2 per cent sodium bicarbonate): the patient receives an enema every other night until five have been given. During treatment by means of enemas oral treatment with carbarsone should be suspended. Enemas are most useful when motile amœbæ are present in the stool.

Toxic effects are rare, but skin rashes and diarrhœa with vague abdominal pains have been reported. Carbarsone is not recommended in the presence of renal or hepatic disease. It is undoubtedly a useful drug for intestinal amœbiasis, especially when given in courses alternating with other amœbicidal drugs. It has also been used locally in the treatment of vaginitis caused by *Trichomonas vaginalis*.

BISMUTH GLYCOLLYLARSANILATE ("Milibis"). This substance is a yellowish-white powder almost insoluble in water. It contains 15 per cent of pentavalent arsenic and 42 per cent of bismuth. The usual route of administration is by mouth and tablets (0.5 G.) are available. Bismuth glycollylarsanilate is poorly absorbed and is largely eliminated in the fæces. The usual course of treatment for intestinal amœbiasis is 0.5 G. 3 times daily for 1 week. This substance is of no value in the treatment of amœbic infection of the liver. The toxic effects are those of the organic arsenicals. Exfoliative dermatitis, agranulocytosis and encephalitis have been reported, but these serious complications are very rare.

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**OXYTETRACYCLINE** ("Terramycin") AND **FUMAGILLIN**. Oxytetracycline has been used alone and in combination with bismuth glycolylarsanilate in the treatment of amœbic dysentery. Antibiotics have been recognised as producing improvement in the clinical condition and in the healing of amœbic ulcers as seen by sigmoidoscopy. These effects may be due to control of intestinal bacteria and many people consider that in treating amœbic dysentery two drugs should be used—one an amœbicide the other acting to suppress the bacillary dysentery which often accompanies amœbic dysentery. *Chlortetracycline* ("Aureomycin") (p. 463) and *fumagillin* (p. 481) have also been used. Fumagillin is an antibiotic isolated from *Aspergillus fumigatus* and is reported to be a most active drug in chronic amœbic dysentery. This antibiotic is amœbicidal and is given in doses of 10 mg. in capsules. A total of 30-60 mg. in divided doses is given daily for 10-14 days. It is of value only in intestinal amœbiasis. Toxic effects have been mild: dizziness, malaise, nausea and vomiting may occur.

**CHLOROQUINE**. Although this drug is chiefly important as a suppressive prophylactic in malaria (p. 557) it is also remarkably effective in the treatment of amœbic hepatitis and abscess of the liver. It is of little value in intestinal amœbiasis. For hepatic infections 1 G. daily for 2 days followed by 0.5 G. daily for 3 weeks is the usual course. The course of chloroquine can be given alternately with emetine therapy: the two drugs should not be given at the same time.

### SUMMARY OF TREATMENT OF AMŒBIASIS

(i) In acute amœbic dysentery *emetine* is unrivalled in giving prompt relief of symptoms: a course lasting not less than 5 days and not more than 10 days should be given. This should be the standard procedure. Several other useful drugs are available, but this does not in itself warrant the devising of complicated schemes of therapy. If the co-existence of bacillary dysentery is clinically apparent it is useful to deal with this by resorting to sulphonamides (phthalylsulphathiazole) or to antibiotics (oxytetracycline), but such measures—especially antibiotics—carry the

risk of side-effects which may prove very irksome. After the course of emetine, the pharmacological attack on the remaining amœbæ can be suitably continued by the relatively mild organic arsenicals *Carbarson* or *Bismuth Glycolylarsanilate*; similarly, topical treatment for the rectum and descending colon is possible by using enemas of *Chiniofon*.

(ii) Hepatitis yields to emetine therapy, but a supplementary course of *Chloroquine* should not be omitted. Even when proof of hepatic damage is not forthcoming, a course of Chloroquine is justifiable as an insurance against late involvement of the liver.

(iii) Cyst carriers should receive a course of *Fumagillin* followed by treatment with *Chloroquine*—the latter again being directed to aborting incipient infection of the liver.

## ANTHELMINTICS

INTRODUCTION. Anthelmintics (antihelminths) are drugs used for the eradication of worms from the body of the host—and the principal hosts are man, domestic animals and livestock. These worms infest higher animals in various ways: they may live in the alimentary canal and they may spend part of their life cycle in the viscera and in other tissues of the body. The development of suitable anthelmintics depends to a large extent on precise knowledge of the life cycle of the individual parasite, and hence in the prevention of infestation the helminthologist's advice is invaluable. If parasites are lying free in the lumen of the bowel or if only loosely attached to the mucosa, it may be fairly easy to poison them with suitable chemicals, and then—by means of a purgative—sweep out the dead or dying worms (and the surplus anthelmintic). An anthelmintic which kills the parasite is called a *vermicide*; if the drug is merely noxious to the worms and causes them to retreat, it is called a *vermifuge*. The desirable anthelmintic is one which has a strong affinity for the parasite, yet does not cause toxic effects if it is absorbed into the blood stream of the host. In some degree nearly all anthelmintics fall short of this requirement: toxic effects are occasionally seen even from therapeutic doses, but allowance must be made for circumstances other than the poisonous

properties of the drug—for example, the presence of fats or alcohol which may expedite its absorption and cause constitutional upset.

The number of people in the world who are infested by parasitic worms are numbered in tens of millions, and the total amount of suffering and disability produced by helminthiasis is beyond computation. It follows that although disinfection is a crude form of therapeutics, judged by the benefits conferred on mankind and on animals, the skilful use of effective anthelmintics is a matter of the highest importance. In public health campaigns designed to disinfest large populations attention must be paid to the safety of the anthelmintic and the effectiveness of a single dose; and the drug must be cheap. There are many places in the world, especially in tropical and subtropical climates, where eight out of ten of the inhabitants are infested by worms—sometimes by several types at once. By comparison, these diseases are seen much less commonly in Britain: threadworm infestation (*oxyuris vermicularis*) is the commonest type of infestation; cases of tapeworm infestation are not uncommon (*T. saginata*—the beef tapeworm and *T. solium*—the pork tapeworm); and roundworm infestation occurs rather less frequently. In this country, hookworm disease (*ankylostomiasis*) is very rarely acquired. All of the worms mentioned above spend part of their life cycle in the human alimentary canal. By contrast the schistosomes and the filariæ produce their characteristic pathological effects through living in the actual tissues of the host. The destructive lesions in schistosomiasis and the mechanical consequences of filariasis are described in textbooks of medicine and pathology.

Man's knowledge of anthelmintics is largely empirical. In the past few decades the actions of the available drugs have been more accurately defined with regard to pharmacology, effectiveness, and toxicity in relation to the host. Further, considerable advances have been made by turning to new synthetic compounds as alternatives to some of the older remedies. The precise mode of action of a drug on a parasite must always be a matter of fundamental importance to the helminthologist and to the pharmacologist. The clinician, however, is chiefly interested in two questions which can be broadly stated thus: (1) Does the anthelmintic

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poison the worms sufficiently to permit of their speedy evacuation from the bowel? (2) Can this be done without unduly upsetting the patient?

The practitioner's list of anthelmintics, drawn up with regard to these issues, is inevitably limited by severely practical considerations. Unless a drug is admissible therapeutically, the precise mode of action on parasites must remain a matter of academic interest. Further, the physician's formulary of anthelmintics is subject to revision, because from time to time new drugs become available which quickly render old ones obsolete (though occasionally the new ones are themselves rejected when their merits have received adequate assessment in practice, for example Diphenan). The ideal anthelmintic would be a "universal" remedy—one that could be used in any type of worm infestation. Such a preparation has not yet been discovered, but it is noteworthy that some chemical substances affect more than one kind of worm.

In the following paragraphs, the various drugs used as anthelmintics are arranged in relation to the particular type of infestation occurring in man. The order in which they are mentioned implies a recommendation of their merits in clinical practice; and precedence is given to infestations commonly seen in this country.

### 1. THREADWORM INFESTATION (OXYURIASIS)

In the treatment of threadworm infestation the general management is at least as important as the selection of the anthelmintic, for it is imperative to prevent reinfestation: this procedure is described in detail in textbooks of therapeutics and nursing. Finger nails should be kept short, hands washed carefully and close-fitting drawers and gloves worn at night. All infested clothing should be boiled daily. A suitable preparation applied to the peri-anal region (weak ammoniated mercury ointment) reduces the risk of migration of worms through the sphincter at night.

**PIPERAZINE.** Piperazine is a white crystalline powder freely soluble in water. Preparations of piperazine phosphate, adipate,



hydrate and citrate are available. These drugs are effective in threadworm infestation (1-2 G. daily in divided doses for 7 days); infants up to the age of 2 years receive 250 mg. twice daily. In ascariasis 4.5 G. is given as a single dose. The drug produces narcosis in roundworms and this effect reaches a maximum after 5 hours. This therefore is an opportune moment for the administration of a saline purgative—to sweep away the worms before they recover. Patients who are heavily infested should receive a second dose of Piperazine after an interval of four weeks. Piperazine is readily absorbed from the bowel but it is not toxic to the host. If ova persist in the stools the treatment can be repeated after an interval of 7 days.

**HEXYLRESORCINOL.** This preparation was formerly used as a urinary antiseptic and in the treatment of infections of skin and mucosa. It is now prescribed almost exclusively as an anthelmintic. It is a crystalline powder, almost white, with a pungent smell and an astringent taste. When used as an anthelmintic, hexylresorcinol should be given in enteric-coated pills. In therapeutic doses it is non-toxic. This drug is active in cases of roundworm and threadworm infestation. Several courses of treatment may be required with this anthelmintic, and the drug can be administered three or four times without danger. It is wise to allow a 3-day interval between courses of treatment. Hexylresorcinol is particularly useful in children and debilitated patients. The drug is given in the morning while the patient is fasting. For adults the total dose is 1 G., for children over 6 years 0.8 G., and for children under 6 years 0.6 G. Hexylresorcinol, if retained in the mouth, is liable to cause shallow ulceration, but in practice this is rarely seen. Two hours after administration of the drug a purgative dose of magnesium sulphate is given, and after 5 hours normal meals may be resumed.

**CRYSTAL VIOLET** (Medicinal Gentian Violet) is the hydrochloride of hexamethylpararosaniline and consists of a greenish-bronze powder or crystals. It is a non-irritant antiseptic especially effective against Gram-positive organisms. It is given in enteric-coated pills to remove threadworms and is occasionally used in

cases of infestation by *Strongyloides stercoralis*. For adults 60 mg. of the drug is given three times daily half an hour before food for 8 days. For a child, 10 mg. for each year of life is given daily in a similar manner, divided into 3 equal doses. Some nausea and diarrhœa may occur in adults. Protective measures against reinfection should be used as described above. In refractory cases, 25 ml. of a 1 per cent aqueous solution of the dye may be introduced into the duodenum by tube daily for 5 consecutive days in adults.

## 2. TAPEWORM INFESTATION ('TÆNIASIS)

**MEPACRINE DIHYDROCHLORIDE.** This antimalarial drug (p. 555), has acquired a considerable reputation as an anthelmintic in tapeworm infestation. The dose is 0·8 G. Few patients readily tolerate this large quantity of mepacrine unless precautions are taken to prevent vomiting. On the day before the drug is to be given, the patient takes a low-residue diet rich in carbohydrate. Preliminary purgation is not necessary. A dose of 50 mg. of chlorpromazine is given at 6 a.m.—the patient fasting. At 8 a.m. mepacrine 0·1 G. in tablet form is taken at intervals of about 2 minutes while he lies comfortably in bed. Frequent sips of water expedite the passage of the drug into the stomach and upper bowel. When the full dose has been taken (8 tablets of 0·1 G.), the patient is instructed to lie quietly in bed on his right side and with his eyes shut. The preliminary medication with chlorpromazine, and insistence on a minimum of physical disturbance are designed to reduce the risk of vomiting. After two hours (at 10 a.m.) a brisk saline purgative is given—say a tablespoonful of Epsom Salts in half a tumbler of water, followed by a pint of hot tea or coffee. The stools are carefully examined for the head of the tape-worm.

**MALE FERN.** The underground stems (rhizomes) of *Dryopteris filix mas*, a common European fern, are collected and dried. The preparation generally used is an ethereal extract of the powdered rhizome. The active principle of male fern is flicic acid. This anthelmintic has an action only on the tapeworm and is not used in any other kind of worm infestation.

The Extract of Male Fern is given in a dose of up to 6 ml. for an adult; this dose should not be exceeded. It can be given as an emulsion with acacia and flavoured with cinnamon or ginger; more conveniently it may be prescribed in gelatin capsules (BPC). On the day before he receives the drug, the patient is allowed only a very light diet of easily assimilable carbohydrate for 12–14 hours. Treatment begins at 6 a.m. with a brisk saline purge (Epsom Salts). The bowel is thus emptied as completely as possible. The drug is then given. The patient continues to fast, and 2 hours later another saline purge is administered. The preliminary purgative is intended to expose the worm to the action of the drug and the second purge removes the worms and the remaining unabsorbed drug. Castor oil must *not* be used as the purgative as the absorption of toxic principles appears to be increased in the presence of oil. The stool passed after the second purgative must be carefully examined for the head of the tapeworm. If the head of the worm is not found, success should not be claimed for the treatment, and after one week the process may be repeated. Male fern is a cumulative poison and this interval of a week must be observed. Therapeutic doses often produce mild side-effects (headache and vertigo) and slight jaundice has been reported. More severe intoxication is manifested by diarrhoea with abdominal pain, nausea and vomiting. Yellow vision and temporary blindness are rare complications. In poisoning with male fern, muscle cramps (salt depletion) sometimes occur: in more severe cases there may be convulsions followed by coma. This drug should not be given to patients who are of poor physique, nor to those suffering from peptic ulcer, cardiac failure, hepatic insufficiency or nephritis; and it should be avoided during pregnancy.

**PELLETIERINE TANNATE.** Pelletierine is an alkaloid and it is named after Pelletier—the French chemist who isolated it from the bark of the pomegranate tree. It is given as the tannate, and is particularly effective in *Tænia solium* infestation. The contra-indications for its use are the same as those described above for male fern: also, the patient is prepared in the same way, using an identical routine of general management. The drug is given as a

single dose (0.25-0.5 G.). Although it has been widely used on the Continent, pelletierine is regarded by British physicians as excessively toxic by comparison with preparations of Male Fern. There is no doubt about its value, but many physicians would reserve it for use exclusively in adults of normal physique. Dizziness is a common side-effect. In frank poisoning, vomiting and diarrhœa lead to severe prostration and intense headache; muscle cramps and paralysis may also develop and if the respiratory muscles are affected this complication may endanger the patient's life.

*Dichlorophen* is exceptional among anthelmintics used in tapeworm infestation in that the worm is killed and undergoes digestion in the patient's alimentary tract. It is often difficult to recognise the worm segments when they are evacuated in the stools and the head (scolex) is rarely identified. In consequence the physician is unable to state that a cure has been effected: if no segments appear in the stools within a month cure is presumed. Dichlorophen should be used only in *T. saginata* infestation. It is contra-indicated if *T. solium* is present because of the danger of auto-infestation with the ova set free.

The patient receives a light carbohydrate diet. Preliminary purging is not necessary. The dose is 70 mg. per Kg. body weight given as a single dose.

### 3. ROUNDWORM INFESTATION (ASCARIASIS)

*Hexylresorcinol* (see p. 570).

*Piperazine* (see p. 569).

**SANTONIN.** Santonin is a white, crystalline substance which is obtained from various Asiatic species of *Artemisia*. On exposure to daylight it turns yellow and is therefore stored in dark bottles. Santonin is non-irritating and almost tasteless. In therapeutic doses, side-effects (if any) involve only the special senses. Xanthopsia is characteristic: white lights—if bright—appear to have a yellow halo. There may also be interference with the sense of taste and of smell. Larger doses cause vomiting and diarrhœa. Finally there is stimulation followed by depression of the cerebral cortex: this results in convulsions followed by coma. Santonin

is used almost exclusively in roundworm infestation. It does not kill the worms, but by acting on the nervous system of the parasite the drug disorganises the musculature. This facilitates expulsion of the worms by purgation. It would appear that in the alimentary canal santonin undergoes a change which makes it toxic to roundworms. The effect is not seen *in vitro*: the parasites survive in the presence of santonin at much higher concentrations than those achieved by full therapeutic doses of the drug. Santonin is absorbed rapidly from the alimentary canal and is excreted in the urine as pigmented substances of unknown composition: this colours the urine deep yellow if it is acid, and red if it is alkaline.

Preliminary starvation is undesirable. Santonin is given at night followed by a saline purgative in the morning. The usual adult dose is 60-200 mg. and the first dose for an adult should not exceed 180 mg. This drug is usually given as a powder. The initial dose for a child should not be more than 60 mg. (10 mg. per year of age). This amount can be administered at night for 2 or 3 consecutive days. Santonin should not be given on an empty stomach and fat should be excluded from the diet before and during santonin medication. These precautions aim at reducing absorption of the drug into the blood stream.

**OIL OF CHENOPODIUM.** Oil of chenopodium is obtained from the plant *Chenopodium ambrosioides*, and the BPC preparation Oil of Chenopodium contains not less than 65 per cent of ascari-dole—its principal constituent. Chenopodium oil is effective against hookworm and ascariasis but in recent years it has given place to anthelmintics which are equally effective and less toxic. The frequency of toxic effects from oil of chenopodium is reduced by combining it with tetrachlorethylene or with carbon tetrachloride.

Chenopodium oil acts as an irritant in the gastro-intestinal tract. It is readily absorbed from the intestine. Full therapeutic doses may cause nausea, vomiting, tinnitus and impaired vision. In overdosage convulsions may occur, followed by depression of the respiratory centre; the drug may cause widespread damage typical of a general tissue poison. It should not be used in patients with renal, cardiac, hepatic or gastro-intestinal disease. The dose

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for an adult is up to 1 ml. given at hourly intervals in gelatin capsules, each containing 0.3 ml. Magnesium sulphate is given one hour after the last dose of chenopodium oil. Preliminary fasting or purgation is not recommended. A high-carbohydrate, high-protein diet given a few days before treatment is a measure which aims at protecting the liver cells.

### 4. HOOKWORM INFESTATION

**TETRACHLORETHYLENE.** Tetrachlorethylene has physical properties resembling those of carbon tetrachloride, but it is much less soluble in water. In the absence of fat in the intestine it is only slightly absorbed. It is not toxic to liver or kidney tissue, and the only side-effects seen with therapeutic doses are giddiness and signs similar to those of alcoholic intoxication. Tetrachlorethylene is a valuable anthelmintic for hookworm infestation. The patient eats a light meal in the evening, avoiding fats. In the morning he takes 3 ml. tetrachlorethylene dispensed in capsules. Two hours later a purgative dose of magnesium sulphate is taken. This drug is the preparation of choice in the treatment of ankylostomiasis.

**CARBON TETRACHLORIDE.** This substance is closely related to chloroform and, as might be expected, it is an irritant when applied to the skin or a mucous membrane. It has a pungent burning taste. The amount absorbed from the intestine varies directly with the duration of stay in the bowel; the physician aims at ensuring adequate exposure of the worms to the lethal effects of the drug, but he must also set a limit to the risk of toxæmia endured by the host—who is the patient under treatment. The presence of fat or alcohol in the intestine significantly increases the absorption of carbon tetrachloride. Carbon tetrachloride can also be absorbed by inhalation. As the conditions governing the absorption of carbon tetrachloride are somewhat unpredictable, its use as an anthelmintic has rightly diminished in recent years.

It is widely employed as a household stain-remover and as an industrial solvent. Acute poisoning can occur from the use of this substance in cleaning clothes in a confined space: the symptoms are headache, dizziness, stupor and then unconsciousness,

followed by death from paralysis of the vital centres in the medulla. Heart failure may occur from the toxic action of carbon tetrachloride on the heart. If large doses of this drug are taken orally the local effects of irritation are almost inevitable—abdominal pain, nausea, vomiting and diarrhoea. If the patient recovers from the immediate effects of severe dehydration and collapse he may yet develop hepatic lesions similar to those caused by chloroform, or a renal lesion which resembles the crush syndrome (lower nephron nephrosis). In chronic poisoning—as from repeated exposure to the drug—the tissue damage is usually seen in the liver, and cirrhosis may follow.

Carbon tetrachloride is a very efficient anthelmintic in hook-worm disease. Further it is cheap. But it is also toxic. It is contra-indicated in poorly nourished patients and in those who suffer from any visceral disease; and it should not be given to alcoholics.

This drug is given in a dose of 0.2 ml. per year of life for a child and a total dose of 3 ml. for adults. The diet before the drug is administered should be low in fat but rich in carbohydrate and protein. The evening before the anthelmintic is given, a light meal only should be taken, and early the next morning the carbon tetrachloride in hard gelatin capsules is taken on an empty stomach. Two hours later the patient is purged—using magnesium sulphate for rapid evacuation. If repetition of this procedure is necessary an interval of 3 weeks should be allowed.

*Oil of Chenopodium.* (see p. 574.)

THYMOL. Thymol is a phenol obtained from the volatile oil of many plants—commonly *Thymus vulgaris*. It is a colourless crystalline substance with a characteristic pungent odour; it is almost insoluble in water. Used externally, it is an efficient antiseptic with a slight surface anodyne action and is commonly used in mouth-washes, gargles and sprays. When taken by mouth, thymol has a burning taste and irritates the gastric and intestinal mucosa. Thymol is readily absorbed. Like phenol, it first stimulates and then depresses the central nervous system. Thus it produces a fleeting phase of excitement with convulsions, and this is followed by depression with drowsiness and coma accompanied

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by paralysis of the vital centres in the medulla. It also has a direct depressant action on heart muscle.

As an anthelmintic thymol is useful only in hookworm infestation. The patient should receive no evening meal: instead a purgative dose of magnesium sulphate is given and this should have acted before the patient retires to bed. The thymol is administered next morning while the patient is fasting. Alcohol and fatty foods are avoided before and during therapy. The dose of thymol for an adult is 3 G. given in doses of 0.5 G. (in gelatin capsules) every 20 or 30 minutes. Two hours after the last dose, a second purge of magnesium sulphate is given. Treatment can be repeated after an interval of one week. The main virtue of thymol is that it is relatively cheap, but it is not regarded as the anthelmintic of choice in ankylostomiasis.

### 5. FILARIAL INFESTATION (FILARIASIS)

**DIETHYLCARBAMAZINE CITRATE.** Diethylcarbamazine citrate is a colourless, crystalline substance very soluble in water, alcohol and chloroform. It is usually administered as Tablets each containing 50 mg. It is relatively non-toxic in therapeutic doses and is used in the treatment of filariasis. In loiasis this treatment kills the microfilariae and the adult worm; but in onchocerciasis, though the drug is toxic to the microfilariae, the adult worm is unaffected. Diethylcarbamazine citrate is given by mouth in a dose of 2 mg. per Kg. three times daily for 2 weeks. The dose is usually increased during this period of treatment: as much as 20 mg. per Kg. body weight may be tolerated. Headache, weakness and nausea may occur as side-effects attributable to the direct effect of the drug. Much more important, however, are the allergic reactions which may follow the release of foreign protein as the worms and larvæ die in the tissues of the host. The onset of such reactions is the signal to stop specific therapy and to turn to the antihistamines as symptomatic remedies. Nodular swellings may be found in the line of the lymphatics where dead worms undergo organisation; and local inflammatory reaction at these sites may be troublesome, calling for the use of sulphonamides or antibiotics.



## 6. SCHISTOSOMAL INFESTATION (SCHISTOSOMIASIS)

LUCANTHONE HYDROCHLORIDE. This substance is a crystalline, orange-yellow powder, given orally as a 500-mg. Tablet in the treatment of schistosomiasis. It is toxic to the adult forms of *Schistosoma hæmatobium* and *S. mansoni*, but it is ineffective against *S. japonicum*. In adequate concentration the parasite is killed, but lower concentrations merely interfere with reproduction and the disappearance of ova from the stools is only temporary. The total daily dose is determined by giving 5 mg. per Kg. body weight: it is administered twice daily for 12 days. Lucanthone is readily absorbed from the bowel and often causes side-effects, especially nausea and vomiting, but minor upsets do not warrant discontinuing treatment. Giddiness, insomnia, tremors, headaches and sweating have also been reported.

*See also* Antimony, p. 545.

## CHAPTER 17

### HEAVY METALS AND METALLOIDS

#### THE HEAVY METALS

THIS description directs attention to certain pharmacological actions shared by the metals silver, lead, aluminium, copper and mercury, and by the metalloids bismuth and arsenic. Many of the salts of the "heavy metals" have similar actions and these may be considered under three headings.

(1) Soluble salts of the heavy metals combine with proteins to form an insoluble precipitate consisting of a metallic salt of the protein with the liberation of acid. If, for example, a solution of lead acetate is added to white of egg, lead albuminate is precipitated and acetic acid is set free. If a suitably weak solution of the metallic salt is used, a pellicle of proteinate forms and this protects underlying tissues from irritation and diminishes secretion. This astringent action can be produced also by vegetable substances which contain tannic acid (p. 424). The more complete the ionisation of the salt, the more rapid is the combination with protein and the more intense the astringent effect: inorganic compounds therefore act more powerfully than the organic ones which are slowly dissociated. The acid ion liberated simultaneously also possesses an astringent action. Thus it is possible, by selecting inorganic salts, to produce on dissociation combined effects of varying intensity. When used appropriately, a solution of lead acetate is a valuable astringent—both ions having a mild action. On the other hand, lead nitrate has an irritant and corrosive action and is therefore potentially dangerous. Thus the same metal attached to different acids may produce effects varying from the astringent action of a solution of lead acetate to the corrosive effect of a solution of lead nitrate. Properties peculiar to the metal also influence the local effect: mercury—as the mercuric ion—is an intensely poisonous substance and destroys cells to which it gains entry; on the other hand lead is a less powerful protoplasmic poison.

Among the factors which contribute to the intensity of the astringent effect are concentration of the salt, temperature of the solution, repeated application, and "vulnerability" of the mucosa (cf. tongue and conjunctiva). Again, the effect on the tissues may be modified by the presence of a layer of insoluble metallic proteinate protecting the surface. If, on the other hand, the proteinate is soluble in excess of protein, the action is not self-limiting and penetration of the superficial tissues results in a corrosive effect.

(2) As might be anticipated from (1) above, the salts of the heavy metals all act in some degree as antiseptics. They precipitate the protein in bacteria, and although their action is slow they are undoubtedly effective in extremely low concentration. This slow but persistent effect is sometimes called an "oligodynamic action". The antiseptic action is naturally proportional to the efficiency of the salt in precipitating protein, and therefore the factors enumerated in (1) above are important here also.

(3) Lastly, the salts of the heavy metals are usually absorbed slowly: they are excreted even more slowly. Cumulative toxic effects are thus liable to occur if these metals (or their salts) are taken over a long time—even in small doses. Their destructive effects on tissues are manifest mainly at the site of absorption and wherever the drug is excreted: thus the alimentary tract and the kidneys are often damaged. In chronic poisoning by heavy metals the functions of the central nervous system are characteristically affected. Clinical syndromes typical of poisoning by the various metals are described, though it is likely that the toxic effects of this group of substances are fundamentally similar—probably depending on interference with various phases of cell metabolism.

SILVER is usually employed therapeutically in the form of Silver Nitrate (lunar caustic). This salt coagulates protein and on application to a mucous membrane forms a white patch of albuminate; the coagulum darkens and becomes grey-black because of its conversion to silver sulphide and silver oxide. Concentrated solutions of silver nitrate or—more conveniently—sticks of the solid substance made by compression, are used as a caustic.

Repeated application may suffice to remove warts; dilute solutions can be used for their astringent action. Silver nitrate (1 per cent) was formerly commonly employed as a prophylactic against gonococcal infection of the infant's eyes—ophthalmia neonatorum: two drops are instilled into the infant's conjunctival sac. Gonococci are promptly destroyed. The astringent action is quickly arrested because the silver nitrate is converted into inert silver chloride. An excess of silver nitrate or the absence of lachrymal secretion may result in superficial damage to the conjunctiva. As a safeguard against this complication, colloidal preparations of silver or silver salts are available. These preparations are non-corrosive. Although their antiseptic action is less powerful than that of silver nitrate, it is strong enough for therapeutic purposes and is more sustained. There are two main types of silver proteinates. The first contains 20 per cent of silver, but as very little of this silver is ionised this substance is relatively non-irritant and does not precipitate chloride. Such a preparation is the Mild Silver Protein of the BPC. The second type contains only 8 per cent of silver, but it is more active because more silver ions are liberated, and a precipitate occurs with chlorides. An example of this type is the official preparation, Silver Protein.

Prolonged use of silver salts topically or internally may result in irreversible pigmentation of the skin and mucosæ. The condition is known clinically as *argyria*: the tissues become slaty-blue in colour. Silver salts are not widely used now in medical practice, but two applications may be mentioned: (1) a stick of silver nitrate is used to touch small ulcers of the buccal mucosa; these recurring and painful lesions can thus be quickly healed. (2) Smokers who wish to wean themselves from the tobacco habit find it easier to do so if a trace of silver nitrate is applied to the tongue before starting to smoke.

**LEAD.** *Lead Subacetate* is a mild astringent. It is still widely used as Goulard's Lotion in the symptomatic treatment of subacute inflammatory conditions of the skin. Lead proteinate is insoluble and there is no risk of absorption through the superficial tissues.

Lead is used extensively in industry and is needed for electric

batteries and a number of manufactured goods such as rubber and glazed pottery. Cases of lead poisoning may occur from the inhalation of lead vapour in these industrial processes and in ship-yards where ships are broken up. Detailed accounts of lead poisoning (plumbism) are to be found in textbooks of medicine and toxicology. The earliest symptoms are loss of appetite, constipation, fatigue, and a metallic taste in the mouth. The patient is pale, and may show a blue line on the gums which results from the formation of lead sulphide. The "lead line" is most obvious in patients who have pyorrhœa alveolaris; it does not occur if the patient is edentulous. Anæmia is a classic sign and punctate basophilia is usually regarded as highly significant. Lead causes spasm in plain muscle and the "lead colic" is usually mid-abdominal with severe pain in the umbilical area. Wrist-drop and foot-drop—with wasting of the muscles of the forearms and legs—are said to be the result of peripheral neuritis almost exclusively motor in character, but there is evidence that lead also has a direct effect on skeletal muscle. The palsy is usually greatest in those muscles which are used most. Thus the painter who develops lead poisoning is apt to develop wrist-drop. Lead encephalopathy is a serious form of poisoning heralded by headaches, sleeplessness and excitability; and these symptoms may progress to hallucinations, convulsions and coma. Chronic plumbism is also an occasional cause of abortion in women.

Nearly all cases of lead poisoning are preventible. Established cases call for careful general management and there may be opportunities for drug therapy—especially in the relief of symptoms. Lead colic is often relieved by the intravenous injection of 10 ml. of 20 per cent calcium gluconate. Many patients find that the discomfort is also reduced by local pressure with the clenched fist and by local application of heat. If these measures fail to abolish pain, hyoscine hydrobromide 0.4 mg. should be injected intravenously. Simultaneously a substantial dose of magnesium sulphate (Epsom Salts) should be given to clear lead salts from the bowel if the metal gained entry by the alimentary canal: the dose is 1 heaped tablespoonful to half a tumbler of warm water followed by a pint of hot tea. Patients suffering from lead encephalopathy causing excitability should be treated with pentobarbitone:

capsules (0.1 G.) are given according to the needs of the individual patient. In the acute stages of the illness it is important to "immobilise" lead which is in the blood and other body fluids. This is best achieved by giving calcium salts in large doses—a teaspoonful of calcium gluconate thrice daily by mouth or 10 ml. of a 10 per cent solution daily intramuscularly. Extra milk (1–2 pints daily) is a valuable source of available calcium. Once the symptoms of acute lead poisoning have lessened, the process of "deleading" the patient should begin. In the state of sustained systemic acidosis, the body's fixed base is called upon as a physiological response, and this has the effect of removing some of the lead stored in bone and muscle. Ammonium chloride is therefore given to create an acidotic state and indirectly promote the excretion of lead. (See also Parathyroid Hormone, p. 389). In modern medical practice it is easier to use a *chelating agent* such as calcium disodium ethylenediamine tetra-acetate (p. 591). This substance has a great affinity for lead and hastens elimination of the metal. The dose is 1 G. administered in 100 ml. 5 per cent dextrose solution intravenously morning and evening. This solution should be given slowly—over a period of about 2 hours. A course of treatment lasts 5 days.

**MERCURY.** The inorganic compounds of mercury, such as the perchloride, were among the first antiseptics to be used; and in modern practice organic mercurials have a place in the list of antiseptics. The mercuric ion precipitates protein. Recently, however, it has been suggested that all dissociable mercurial compounds act by virtue of a single basic mechanism. The mercuric ion readily reacts with sulphhydryl groups to form preparations called mercaptides. Even in low concentration mercurials are able to inactivate sulphhydryl-containing enzymes and thus interfere with cellular metabolism and function. The various therapeutic actions of the mercurials can be related to differences in the chemical configuration of the mercury-containing compounds. These affect solubility, dissociation, relative affinity for various cellular receptors, the distribution of the mercurial throughout the body, and its excretion. The organic mercurial diuretics, for example, have very low dissociation constants and

are excreted by the kidney. As a result an effective concentration of mercury ions is attained only in the kidney. The result is that in the renal tubules sulphhydryl enzymes—which are essential for tubular reabsorption—are temporarily inhibited by the mercury and thus diuresis results. In different circumstances, when an insoluble mercurial compound such as mercurous chloride (calomel) is taken by mouth a significant concentration of ionic mercury is attained only in the bowel. Here again active processes of absorption are inhibited in the mucosa and a fluid motion is evacuated. Again, when certain organic mercurials such as mercurochrome are applied locally to infected areas of skin or mucous membrane, the sulphhydryl receptors of the micro-organisms are inhibited; and as these appear to be more sensitive than those of the host the bacteria are killed without perceptible harm to the patient.

Metallic mercury, kept in a finely divided state by trituration with chalk, was formerly given by mouth as Grey Powder. A minute amount of mercury, converted to soluble proteinate, was absorbed and produced the same effect as calomel. These matters are now of limited importance as laxatives much safer than the mercurials are readily available.

When the metal is finely divided and dispersed in a suitable oily vehicle, mercury can be injected intramuscularly. An ointment of ammoniated mercury can also be used for inunction. Most of the metal absorbed during inunction gains entry to the body through the lungs: mercury volatilises under these conditions and is inhaled. It must be stressed that these phenomena are now of limited interest in therapeutics, but they retain their importance in relation to industrial poisoning and to toxicology generally. After absorption mercury is stored in liver and kidney. It is excreted slowly—most of it in the urine. It also appears in the saliva and may cause severe sialorrhœa, and stomatitis may develop.

Mercury salts are occasionally used as purgatives and as disinfectants. Their use in the treatment of syphilis is now only of historical interest.

A large dose of a soluble salt such as mercuric chloride (corrosive sublimate) by the mouth acts as a corrosive poison. The

mucous membrane in the mouth, throat and stomach is promptly destroyed. There is intractable vomiting accompanied by great pain. The patient is shocked and dehydrated. Acute nephritis is almost inevitable, and complete anuria is a contributory cause of death.

Chronic mercury poisoning from cumulation of repeated small doses is the type seen in industry. It usually results from continual inhalation of volatilised mercury. This industrial hazard occurs in the production of mercury and its derivatives, the manufacture of thermometers and barometers, the manufacture of detonators containing mercury, and in the making of felt hats.

The symptoms of chronic mercury poisoning are excessive salivation with a metallic taste in the mouth, loosening of the teeth with painful inflamed gums, and occasionally a line on the gums as with lead poisoning. Loss of appetite, indigestion and diarrhoea are common. Irritation of the skin may occur and there may be penetrating ulcers on the finger-nails and knuckles. Nephritis is a serious complication and renal insufficiency may progress to uræmia. Erethism, a peculiar disturbance of the nervous system characterised by shyness, irritability, tremor and insomnia may occur. The tremor may be so marked that assistance may be required in eating.

As with chronic lead poisoning preventive measures are all-important. The volatilisation of mercury is prevented by limiting the area of the metal exposed to the atmosphere and by keeping workrooms cool. Constant care in the handling of mercury and high standards of personal hygiene are essential: in particular the teeth must be kept clean and regular dental care is imperative.

Treatment of chronic mercurial poisoning consists in removing the patient from exposure to mercury and in promoting elimination of the mercury by bowels and kidneys. Dry extract of belladonna 30 mg. thrice daily relieves the excessive salivation. Mercury dermatitis may be prevented or alleviated by the application of a 10 per cent solution of sodium hyposulphite. In acute mercury poisoning Dimercaprol (p. 590) should be used, but it is less effective in chronic poisoning.

**COPPER.** Copper is a normal constituent of the body tissues; but only minute quantities are needed, and the amount contained in a normal mixed diet is adequate for health. It is unlikely that



copper deficiency ever occurs in adult life. On the other hand, infants on a milk diet may occasionally suffer from copper deficiency and in consequence develop a rare type of nutritional anæmia. In such circumstances it would be rational to prescribe a preparation of iron containing a trace of copper sulphate. With this exception copper is not necessary for the treatment of anæmia. Copper Sulphate in solid form is a caustic and is used to control exuberant granulation tissue. The synonym Blue Vitriol is significant of its chemical origin and its potency. A 1 per cent solution of copper sulphate was formerly used as an emetic: safer alternatives are now preferred, such as a dessertspoonful of common salt in a tumbler of luke-warm water. Copper sulphate is an antidote in phosphorus poisoning, producing the insoluble copper phosphide. Phosphorus poisoning is rarely encountered in general practice.

**ZINC.** Zinc salts are employed in medicine for their local actions. A solution of 1 per cent zinc sulphate is a fairly mild astringent and a local antiseptic; strong solutions can, in some circumstances, produce corrosion. A very dilute solution of zinc sulphate (0.25-0.5 per cent) is used in conjunctivitis. *Zinc oxide*, *zinc carbonate* (calamine) and *zinc stearate* are, for practical purposes, insoluble and are therefore suitable constituents of dusting powders: they keep the skin dry and act as lubricant-protectives to skin surfaces which are in contact (breasts, buttocks, skin creases). An inflamed skin (sunburn) can be dusted with these insoluble powders: alternatively they can be used in lotions—to provide also the temporary cooling effect which accompanies evaporation of water; the insoluble powder remains at the site of application. It is possible that a trace of the zinc salt slowly combines with protein in the superficial layers of the skin and results in a mildly astringent action, but this cannot be an immediate effect. Simple dusting powders and Calamine Lotion are widely used as domestic remedies and are undoubtedly valuable as palliatives when the skin is itching and irritable. *Zinc sulphate* as an astringent lotion can also be used as a simple 1 per cent solution when a skin surface is “weeping”—circumstances which make the use of dusting powders inappropriate because of

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“caking”. Other preparations containing zinc oxide for application to the skin are Zinc Paste which contains 25 per cent of zinc oxide and 25 per cent of starch in soft paraffin; and Unna’s paste is composed of 15 per cent zinc oxide with gelatin and glycerin.

ALUMINIUM. *Alum*, which may be either potassium aluminium sulphate or ammonium aluminium sulphate, is used as a mild astringent-antiseptic preparation for application to mucous membranes. It is also used in 1 per cent solution as a wash to diminish excessive mucous secretion.

*Aluminium hydroxide* and *aluminium phosphate* are used as antacids to reduce gastric hyperchlorhydria (p. 406). *Kaolin* consists largely of aluminium silicate. It is an insoluble powder and is used as an adsorptive—as it shares this peculiar physical property with Active Carbon. Thus it is very commonly used in suspension or as a powder to combat mild attacks of enteritis, and the dose is 1–2 teaspoonfuls every 2 hours. Nearly all cases of “mild enteritis” are in fact caused by dysentery bacilli, and it is therefore justifiable to use sulphonamides (p. 509) in preference to kaolin—which in this context has a rather doubtful status therapeutically. If poultices are to be used at all, Kaolin Poultice is probably the preparation of choice. It contains kaolin, boric acid, thymol, methyl salicylate, oil of peppermint and glycerin. The glycerin improves the consistence of the poultice and prevents drying. Inclusion of the other ingredients is said to be justified by their antiseptic and counter-irritant actions; but the clinical circumstances rarely warrant the use of antiseptics on the skin, and in this preparation their effects as counter-irritants are negligible. If the patient benefits at all, it is probably from the comfort derived from *heat*; and the smell of the poultice brings reassurance.

THALLIUM. *Thallium acetate* when given by mouth produces, after a latent interval of about 2 weeks, epilation of the scalp. It is used to rid the scalp of infected hair in the treatment of ring-worm in children. The dose must be accurately calculated and is 8·5 mg. of thallium acetate for each kilogram of naked body-

weight. This calculated amount is given in a single dose and it is not repeated. After 3 days, temporary lassitude develops and there are "rheumatic" pains in the legs in about one-third of children. These symptoms pass off in a few days and from 17-21 days after administration of the drug the hair begins to fall out. Thallium should never be given to adolescents, or to adults or children over 30 Kg. in weight, because severe toxic symptoms may result from the doses required. After epilation the hair grows in again. Toxic effects include vomiting, albuminuria, ataxia and coma. Permanent damage to the central nervous system has caused blindness. Deaths have been reported following thallium epilation.

ARSENIC (Arsenious Oxide,  $\text{As}_2\text{O}_3$ ). The actions of arsenic have been discussed above (p. 579). Preparations of arsenic are now of toxicological rather than therapeutic interest.

Industrial arsenic poisoning is seen in chemical works, in glass making and cadmium plating, in agricultural spraying and in the use of sheep dip. In *acute poisoning* with a single large dose of arsenic, after a latent period of half an hour there ensues a feeling of tightness in the throat, abdominal pain and vomiting. The act of vomiting, by evacuating most of the poison, may save the patient's life. The main effect, however, is the production of diarrhoea, with watery motions containing shreds of mucous membrane. The patient becomes dehydrated, cold and shocked. Intense thirst is characteristic. Death may occur within 48 hours.

The early symptoms of *chronic poisoning* are attacks of vomiting and diarrhoea. Arsenic Trioxide has a sweetish taste and its presence in food may not be noticed. The alimentary disturbances are therefore commonly misdiagnosed. The patient may also feel as if he had a common cold—with running at the nose and a sense of fullness in the head. At a more advanced stage there is pigmentation of the skin and hyperkeratosis of the palms and soles. Arsenical peripheral neuritis closely resembles that associated with chronic alcoholism. Other symptoms referable to the nervous system include headache, drowsiness and impairment of mental activity.

The treatment of chronic poisoning consists in removal of the patient from further exposure. Dimercaprol has greatly improved the prognosis. Its action and dosage are discussed below. It is

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reported that aneurine 100 mg. given daily intramuscularly hastens recovery from the effects of peripheral neuritis.

Arsine poisoning occurs in chemical and galvanizing works, in submarines and in the preparation of hydrogen for balloon inflation. The essential toxicological effect is the production of acute hæmolytic anæmia. Within six hours of exposure malaise, headache, nausea and vomiting develop followed by abdominal pain and diarrhœa; later the characteristic signs develop—hæmoglobinuria or hæmaturia. Within 48 hours jaundice, cyanosis and oliguria may be present. Severe anæmia is frequently noted accompanied by leucocytosis. In the treatment of arsine poisoning oxygen should be administered as soon as possible. Blood transfusions are almost invariably needed.

**BISMUTH.** The status of the insoluble bismuth salts in the treatment of peptic ulcer is mentioned above (p. 412). Bismuth sodium tartrate is an example of a soluble salt. If bismuth salts are given orally they are not absorbed; and even a soluble salt is converted into an insoluble one. Intramuscular injection is the only reliable method of administration in order to obtain the systemic action of bismuth.

The BPC preparation Paste of Bismuth Subnitrate and Iodoform (BIPP), was formerly used as a compound antiseptic of convenient consistence for introduction into infected fistulæ and ulcers. Its use was largely abandoned after the occurrence of cases of iodoform poisoning. Salts such as bismuth carbonate are said to protect the mucous membranes of the stomach and intestine if these are inflamed. Radiological observations, however, have failed to support the view that "coating" the gastric mucosa can play a significant part in the therapeutic effects claimed for bismuth carbonate. It would appear that the salt is fairly rapidly removed from a normally functioning mucous membrane, and it is probable that an irritable or inflamed mucosa will remove the particles of bismuth carbonate even more rapidly. The main use of bismuth is in the treatment of syphilis, particularly when it is desired to avoid the risk of a Jarisch-Herxheimer reaction (p. 541). The mainstay of therapeutics in syphilis is penicillin, but some physicians are disposed to supplement the antibiotic by giving a course of injections of bismuth intramuscularly—at the end of

the penicillin treatment. If too much bismuth is injected or if signs of cumulation develop, the toxic effects resemble those caused by mercury. Stomatitis, a blue line in the gums, nephritis and skin rashes may occur. The treatment consists in the administration of dimercaprol (see below).

**DIMERCAPROL** (British Anti-Lewisite; BAL). This compound, 2:3-dimercaptopropanol, is used in the treatment of certain types of heavy metal poisoning. Heavy metals interfere with the sulphhydryl groups which are indispensable to the functioning of enzyme systems of proteins in living cells. Dimercaprol is a compound which has sulphhydryl groups to offer. Hence, if this substance is present in body tissues it may satisfy the affinity of the heavy metal for sulphhydryl groups and so indirectly protect the enzyme systems of the tissue cells.

The compound formed by the heavy metal and the di-thiol, dimercaprol, is relatively stable and is excreted without causing damage to the excretory mechanism (kidney, liver, etc.). As dissociation of the compound can occur it is important to give sufficient dimercaprol to ensure that the amount available is in excess of requirements.

Dimercaprol is given intramuscularly as a 5 per cent solution in arachis oil with benzyl benzoate. Success depends on early treatment and the toxic complications of arsenic, mercury, gold, antimony and bismuth have been relieved by this drug, with the exception of aplastic anæmia which does not respond to treatment with dimercaprol. In severe poisoning 3 mg. of dimercaprol per kilogram of body weight (200 mg. for an average adult) should be given every 4 hours for the first 2 days followed by less frequent injections for 10 days. The drug may cause nausea, vomiting, lachrymation, with burning sensations in mouth, throat and eyes. These side-effects generally develop rapidly within 15 minutes of injection and subside within a few hours.

**CHELATING AGENTS.** These substances form a firm non-ionized cyclic complex (chelate) with cations. Such compounds can form stable, soluble, non-toxic complexes with calcium and certain heavy metals.

*Ethylenediamine Tetra-acetic Acid (EDTA)* is one such chelating agent. It is an insoluble crystalline powder. The calcium compound, calcium disodium ethylenediamine tetra-acetate ("Calcium Disodium Versenate") is soluble and has a great affinity for lead. There is a great variation in the binding capacity of EDTA for different cations: for example if the calcium complex of EDTA is exposed to lead, the lead complex of EDTA will be formed and calcium will be released. The harmless lead complex is then excreted in the urine. It is therefore a most important preparation in the treatment of lead poisoning; and administered to such patients it increases the urinary secretion of lead more than any other known agent. In man a fall in blood pressure occurs during rapid intravenous injection. Calcium disodium ethylenediamine tetra-acetate combines also with certain other metals, for example iron, copper and magnesium. *Short courses* of treatment are advised in order to minimise the danger of depleting the body of metallic ions essential to metabolism. In lead poisoning the calcium complex of EDTA (dispensed in 5 ml. ampoules of 20 per cent solution) is given by slow intravenous infusion in isotonic glucose solution. The usual adult dose is 1 G. twice daily for periods up to 5 days. After an interval of 2 days, this course of treatment may be repeated. The tetrasodium salt of EDTA given intravenously lowers the calcium level of the plasma and produces hypocalcæmic tetany. It is reported to be effective in treating hypercalcæmia.

The fixation of the available calcium in the blood by chelating agents has led to the widespread use of these preparations in laboratory practice as a means of preventing blood coagulation *in vitro*.

## CHAPTER 18

# CHEMOTHERAPEUTIC AGENTS IN MALIGNANT AND ALLIED DISEASES

**INTRODUCTION.** The management of patients at various stages of malignant disease covers a wide field of therapeutics, including the skills of nursing. Maintenance of physical and psychological health ("morale"); the relief of pain, anxiety and insomnia; and the use of blood transfusion, are among the many important procedures employed. Therapeutic measures which aim at the elimination of the growth itself are often crude: this is almost inevitable while our understanding of malignant disease has such serious limitations. Surgical excision of the tumour and the surrounding tissues or destruction of the growth by means of X-radiation are the current procedures. It would be much more satisfactory if drugs were available with a selective inhibitory action on the cells of a malignant tumour. Very few substances are in fact known which can be used therapeutically in this way: a few compounds are on trial and these are discussed below. They are used in a limited number of conditions grouped under "malignant disease", namely, neoplastic diseases of the blood and reticulo-endothelial system, cancer of the breast, cancer of the prostate and anaplastic bronchial carcinoma.

The therapeutic agents which have a direct effect on malignant cells may be roughly classified according to their mode of action.

1. Substances which inhibit cell division—the mitotic poisons. The most important members of this group are the nitrogen mustards and their analogues which have an action against dividing cells similar to that of irradiation; they are often called "radio-mimetic" substances. There are many other mitotic poisons with diverse modes of action but they are not readily subject to classification.

2. Substances which act as competitive inhibitors in cellular

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nucleic acid metabolism. These are often called "antimetabolic" agents.

3. Hormones which by altering the endocrine environment of neoplastic cells inhibit their growth.

4. Radio-active isotopes may be valuable if they are so concentrated in neoplastic cells as to deliver large doses of radiation to them without producing harmful effects elsewhere in the body.

As yet no *qualitative* differences have been discovered in the metabolic processes of neoplastic tissue. With the exception of the radio-active isotopes, the drugs used in the treatment of malignant disease exploit the quantitative differences between the metabolism of neoplastic cells and normal cells. These differences are essentially the differences between actively multiplying cells and cells which are dividing less rapidly. It follows that one of the hazards inseparable from the use of these drugs is that those body tissues which *normally* undergo rapid division will also be affected. Thus toxic effects are most frequently seen in bone marrow, lymphoid tissue, the alimentary epithelium, the skin and its appendages.

## NITROGEN MUSTARD AND ITS ANALOGUES

The nitrogen mustards were introduced as war gases and were first used by the German Army in 1917. The military value of these poisonous gases lay in the fact that they resulted immediately in a large number of casualties: they had strong vesicant action on the skin, the corneal epithelium and the mucosa of the respiratory tract. Later it became obvious that soldiers who were convalescing from these "traumatic" effects often developed constitutional illness—presumed to be late effects due to absorption of the poisonous gas. In fatal cases it was discovered that there were histological changes which readily accounted for these symptoms: they were seen in the bone marrow, lymphoid tissue and in the epithelium of the alimentary canal. Further investigation revealed and defined the cytotoxic action of nitrogen mustard, but it was not until 1942 that it was first used in treatment of malignant disease in man. Many derivatives of nitrogen mustard have been synthesised; few seem to have any advantage over di(2-chloroethyl) methylamine (Mustine).



All derivatives have a mode of action similar to that of mustine, but they differ in the route of administration and rate of action.

When a nitrogen mustard goes into solution, intramolecular transformation of the chloro-ethylamine side-chains takes place with the formation of a cyclical ethylenimonium derivative which is strongly ionised. This compound is highly reactive and combines freely with a large number of inorganic and organic radicles, including cellular nucleic acids. Finally an inactive dihydroxy compound is formed and excreted. Different mustards vary in the rate with which the cyclical compound is formed. The action of nitrogen mustards on cells is non-specific and depends on the reaction of the ionised complex with nuclear chromatin; rapidly dividing malignant cells are affected most, but the therapeutic index is low ("latitude of therapeutic action") and bone marrow depression is readily produced. The results of the reaction of the nitrogen mustard with the cell appear slowly, but they are long lasting. Cell division is inhibited at a premitotic phase, though mitosis already started is normally completed. Very primitive undifferentiated cells such as the hæmocytoblast are not affected by nitrogen mustards and survive normally, though their division is arrested. For this reason nitrogen mustards are of no value in acute leukaemias. After the interference with mitosis nuclear degeneration occurs, and cell death follows. This is not accompanied by a tissue reaction. In sublethal doses nitrogen mustards are strongly mutagenic.

Minor though serious toxic effects of nitrogen mustards are due to their strong local irritant action. Even forms suitable for oral administration are very prone to produce gastro-intestinal irritation. Mustine can be given only by intravenous injection and is liable to produce local venous thrombosis. Extravasation into the subcutaneous tissues results in the formation of a necrotic slough. Lachrymation, miosis (small pupils), sialorrhœa, increased bronchial secretion and colonic stimulation may be produced by nitrogen mustard therapy, and it is thought that this may be because of the marked chemical similarity between the final transformation product and acetylcholine. Vomiting is a prominent and troublesome side-effect even with parenterally administered nitrogen mustard; it is thought to be due to a central

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stimulant action. The major toxic effect of nitrogen mustard therapy is depression of the bone marrow; if sufficient overdose is given, gastro-intestinal symptoms may be produced, following damage to the alimentary epithelium. Bone-marrow depression is usually transient and complete recovery is the rule, but it is regarded as a sign of serious overdosage. Recovery from this usually begins within a few weeks and is complete within a few months.

Mustine forms a water-soluble hydrochloride; it is a white crystalline compound. Because of its intense chemical reactivity in solution, it should be stored dry until immediately before use when it is dissolved in normal saline. It should be given intravenously, preferably by injection into the rubber tubing of a fast-running intravenous saline infusion. If directly injected into the vein, especially when the blood-flow is sluggish (as it may be for example in mediastinal obstruction), venous thrombosis is liable to occur. Because of the frequency of nausea and vomiting, the patient should receive premedication with a barbiturate and an anti-emetic agent such as chlorpromazine. In malignant effusions of the serous sacs nitrogen mustard may be injected directly into the pleura, peritoneum or pericardium, provided that the effusion is not loculated.

Mustine hydrochloride has a beneficial effect in lymphatic leukaemia and in Hodgkin's disease, especially where the disease is generalised and systemic upset is marked. Localised disease should be treated by radiotherapy. Drug resistance to nitrogen mustard eventually appears, but is not accompanied by cross-resistance to irradiation. Undifferentiated bronchial neoplasms may be sensitive to nitrogen mustards. In these cases the treatment is sometimes particularly effective when obstructive symptoms are present. When the malignant cells die, the tumour tends to shrink in size immediately rather than to show an initial increase as is liable to happen after irradiation; hence symptoms and signs which are caused by obstruction are likely to be relieved; the danger of aggravation is very slight.

CHLORAMBUCIL is a nitrogen mustard derivative. It is adequately absorbed when given orally, and in the normal range of dose

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employed is not irritant to the alimentary tract. Its pharmacological action, side-effects and toxic effects resemble those of mustine. It is of value in the treatment of chronic lymphatic leukæmia and Hodgkin's disease. Compared with mustine given intravenously the action of chlorambucil is slower in onset and the effects are less dramatic. Chlorambucil is therefore used when there is no urgency and when it is essential to avoid intravenous administration. It is of no value in bronchial carcinoma.

### BUSULPHAN

Busulphan is a sulphuric acid ester which forms an ionised cyclical compound with actions similar to those of nitrogen mustard. It is unique in that its effect seems virtually restricted to the bone marrow, and particularly to the myeloid series of cells. It has a useful place in the treatment of chronic myeloid leukæmia. Platelet precursors are only slightly less sensitive than the polymorphonuclear leucocytes and, though in therapeutic doses myeloid tissue alone is depressed, very slight overdose may cause thrombocytopenia. In severe overdose erythropoiesis is also depressed, but no other tissue is affected. When given by mouth Busulphan is well absorbed and therapeutically effective. In the treatment of leukæmia it may precipitate excessive urate excretion following massive breakdown of white cells, and this may cause urinary symptoms.

### TRETAMINE

Tretamine (Triethylene Melamine; TEM) was introduced as a "finisher" in the textile industry, where its activity depended on its ability to form cyclical compounds. It forms these compounds in the human body, and has an action similar to that of the nitrogen mustards. It is usually given orally, but the rate of absorption is variable. The therapeutic applications of tretamine are similar to those of the nitrogen mustards. As it is a cumulative drug there is difficulty in determining the dose and toxic effects are common. Marrow depression is readily induced and this complication may be delayed in appearance. It is not recommended for therapeutic use.

## OTHER MITOTIC POISONS

COLCHICINE, an alkaloid used in the treatment of acute gout (p. 271) is a mitotic poison, acting against the spindle of cells in mitosis and producing mitotic arrest in metaphase. A much less toxic derivative *Demecolcine* seems to have a particularly pronounced effect on myeloid tissues, and is used as a therapeutic agent in chronic myeloid leukæmia. It is ordinarily given by mouth, but in severe cases it may be given intravenously for the first few days. Demecolcine is liable to produce gastro-intestinal irritation. There are few major toxic effects.

URETHANE (ethyl carbamide, p. 219) which was introduced as a hypnotic now remains as an agent of some value in the treatment of multiple myelomatosis. It produces chromosomal breaks and interferes with cell division in marrow and in the tissues of the alimentary tract. Its precise mode of action is not known. Urethane is given by mouth in doses of 1 G. thrice daily. It is liable to cause nausea and vomiting, and drowsiness is a frequent side-effect. Marrow depression may occur. It is the drug of choice in the treatment of multiple myelomatosis; it does not cure the disease, but it often brings about considerable clinical improvement in so far as it sometimes relieves bone pains in this disease.

*Arsenic* (arsenic trioxide) is a non-specific cellular poison and was formerly used in the treatment of chronic leukæmias. It is toxic, and as a drug it is unsatisfactory; it is obsolete.

## THE ANTIMETABOLIC AGENTS

This group comprises 6-mercaptopurine and the folic acid antagonists—aminopterin, amethopterin and amino-an-fol. They are of value only in the treatment of acute leukæmia. They act by depressing nucleic acid metabolism in the dividing cell by a process of competitive inhibition: 6-mercaptopurine probably replaces adenine or hypoxanthine; and the folic acid antagonists oppose the action of folic and folinic acids. Mitosis is not prevented, but tends to be arrested in metaphase. All dividing cells are affected, hence the major toxic actions are on the bone marrow

and alimentary epithelium. In overdose a pancytopenia and a hæmorrhagic enteritis may be produced. Alimentary tract symptoms are less severe with 6-mercaptopurine. Lymphoid tissue undergoes involution but does not become aplastic. Both 6-mercaptopurine and the folic acid antagonists are well absorbed by mouth, and both are largely excreted by the kidney, though a considerable proportion of 6-mercaptopurine is retained and incorporated into the cellular nucleic acids.

6-Mercaptopurine and the folic acid antagonists should be reserved for the treatment of acute leukæmia. The folic acid antagonists are generally more successful in acute lymphatic leukæmia in children, and of much less value in other acute leukæmias. 6-Mercaptopurine is generally effective in all types of acute leukæmia, myeloid, lymphatic and monocytic; and the results of treatment are better in children. During treatment it may be necessary to continue with these drugs despite evidence of bone-marrow depression; this risk may be justified by results but if thrombocytopenia becomes severe treatment must be stopped, as there is no effective therapy for platelet deficiency. Leukæmic tissues eventually acquire resistance to both 6-mercaptopurine and folic acid antagonists, but cross-resistance to both agents does not develop, and when one is no longer of value the other may induce remission. They are not synergistic: they should therefore be employed one after the other and should not be used together. Though neither is curative both are valuable palliative agents and may produce significant prolongation of life.

#### HORMONAL THERAPY IN MALIGNANT DISEASE

The course of two types of malignant disease may be significantly altered by hormone therapy. Acute leukæmia usually undergoes a short-lived remission if a state of hyperadrenalcorticism is induced; mammary and prostatic cancer may be controlled for considerable periods of time by alteration of the sex hormone status.

**ACUTE LEUKÆMIA.** In acute leukæmia, especially in children, treatment with either ACTH or adrenal cortical steroids will commonly induce remission of the disease. The mechanism whereby this is brought about is not understood. When a patient

proves to be amenable to this treatment the response occurs promptly. Unfortunately, improvement lasts only a short time: the leukæmic tissues rapidly become resistant to the effects of the steroids. Initially full doses should be used. The various preparations available are all effective therapeutically, but for ease of administration those given by mouth are generally employed; and prednisone or prednisolone are to be preferred as they cause less salt and water retention. The initial full dose should be reduced only when a response has occurred, or when it is clear that no response can be expected. When a remission occurs—as it usually does within two weeks—the dose of the steroid should be reduced to a level which suffices to control the manifestations of the disease, but which is not likely to cause side-effects. A steroid-induced remission may be apparently complete, but relapse is inevitable and most often occurs within two or three months. Steroid therapy should be reserved for acutely ill patients in whom there is no time to wait for response to 6-mercaptopurine or to folic acid antagonists. The number of drugs available for the treatment of acute leukæmia is very limited. When, therefore, steroids are given they should be used alone, and no other drug should be given until relapse from steroid-induced remission is beginning.

**PROSTATIC AND MAMMARY CANCER.** The normal development of prostatic and mammary tissues is a secondary sex character and is dependent upon adequate supplies of the appropriate sex hormones. If the secretion of these hormones fails, the tissues of the breast and the prostate undergo involution. Prostatic and mammary tissues which are neoplastic also show this “hormone dependence”; and this is the basis of endocrine therapy. Hormone therapy is established as a valuable form of treatment, especially in prostatic cancer. In this condition surgical removal of the growth is rarely undertaken; surgery is usually restricted to relieving the effects of obstruction. If the output of androgen can be reduced a remission of the disease is usually obtained: orchidectomy is the obvious procedure for attaining this effect. In practice, however, the administration of oestrogens to patients suffering from prostatic cancer usually suffices to cause remarkable improvement. When orchidectomy is carried out, the sub-

sequent administration of œstrogens often effects further clinical improvement by their direct depressant action on the neoplastic cells in the prostate. Side-effects in the form of mild feminisation are invariable. Impotence, loss of libido, and gynæcomastia occur frequently. A synthetic œstrogen suitable for oral administration should be used. The absence of side-effects is an important factor in the choice. The synthetic preparation is inexpensive, and stilbœstrol is usually satisfactory. Relapse eventually occurs, but the disease may remain under therapeutic control for several years.

In cancer of the breast hormone therapy is also important. Here, however, surgical ablation of the ovaries and the adrenals is an important preliminary procedure. Such treatment is reserved for patients suffering from advanced carcinomatosis who require palliative measures.

In postmenopausal women œstrogen therapy may be helpful in treating metastatic lesions of the soft tissues, but the ultimate results are disappointing. Androgens may be given at any age, and have been found to be of greatest value in producing signs of regression and symptomatic relief in osseous metastases.

œEstrogens and androgens should be given in high dosage; the effects of treatment are usually slow to appear. Maintenance therapy is essential. The important side-effects of androgens are summed up in the word "masculinisation"; and with œstrogen therapy uterine bleeding may occur.

**RADIO-ACTIVE ISOTOPES.** Two isotopes have an established place in the *treatment* of malignant disease. They are  $^{131}\text{I}$  in carcinoma of the thyroid and  $^{32}\text{P}$  in polycythæmia vera and myeloid leukaemia. Their peculiar values lie in the fact that they are selectively localised in the malignant tissue and therefore deliver to it a large dose of irradiation without significantly affecting other tissues in this way.  $^{131}\text{I}$  as a diagnostic and therapeutic agent is mentioned elsewhere (p. 635).  $^{32}\text{P}$  is an emitter of high-energy  $\beta$ -irradiation with a penetration of only 2–7 mm. The half-life is 14.3 days. It is prepared as the sodium salts of phosphoric acid. It is well absorbed by mouth but is commonly given intravenously in order that dosage may be as accurate as possible. Within

#### CHEMOTHERAPEUTIC AGENTS IN MALIGNANT DISEASES

one week 50 per cent is excreted in the urine, but excretion thereafter is slow. Actively growing tissues selectively concentrate radio-phosphorus: in its final distribution the greatest quantities are found in the bone marrow. Overdose produces bone-marrow depression. In the treatment of myeloid leukæmia and polycythæmia vera, irradiation is selectively given to the abnormal bone marrow. The response is related to the dose in a roughly quantitative fashion—hence the dose required can be calculated satisfactorily from the effect of a preliminary small dose.

RADIO-ACTIVE GOLD in colloidal suspension may be used in the palliative treatment of metastatic malignant disease of serous sacs. With this treatment it is found that effusions into the serous sacs of the body occur less frequently. Radio-active colloidal gold is, however, a source of strong irradiation and requires special precautions in handling. Its use is therefore much restricted.



## CHAPTER 19

# DRUGS ACTING LOCALLY

### INTRODUCTION

MANY of the drugs mentioned in this chapter are well-known domestic remedies. Their importance should not be under-rated. When they are used intelligently under medical supervision and with a clear understanding of those physical and chemical properties which determine their therapeutic applications, these substances confer remarkable benefits. Preparations such as dusting powders, soap, the vegetable and mineral oils, glycerin, alcohol, etc., used in the simple procedures of body-hygiene or as preparations needed in the treatment of disabilities caused by skin disorders, are of great importance. For various reasons attention is usually focused on new inventions—in this context new drugs for the treatment of comparatively rare diseases. There is nothing to be gained by decrying the importance of genuine advances which provide new pharmaceutical preparations which are of proved therapeutic value. But there is also an obligation on the student and the practitioner to remember that the skilful use of simple medicaments can prevent major illnesses which call for complicated therapeutic measures and the services of nurses and medical specialists. The historical aspects of this subject should not be overlooked. For example, it may well be that the prophylactic use of such ancient remedies as starch, talc and zinc oxide to prevent the ill-effects of excessive sweating has been of greater significance to mankind—in terms of the prevention of suffering and morbidity—than the introduction of the steroid hormones as therapeutic agents. At all events it is beyond dispute that these simple substances are of capital importance to the medical practitioner who has the responsibility of prescribing drugs for the relief of ailments which may be commonplace but which nevertheless result in serious disability.

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### EXTERNAL PROTECTIVES AND EMOLLIENTS

**PROTECTIVES** are drugs which form a superficial covering over the skin, to protect it from contact with cold and dry air, strong sunlight, or micro-organisms, and check the evaporation of water from the epithelial cells. They are also used to absorb sweat, and by keeping the skin dry they prevent the ill-effects of maceration of the stratum corneum (excoriation, infection, painful friction, etc.). Protectives are used in the form of insoluble dusting powders: the common ingredients are chalk, starch, magnesium silicate (French chalk) and zinc oxide. Several of these pharmaceutical preparations are often compounded together and they may be made more acceptable for general purposes if they are faintly scented by the addition of a trace of essential oil (such as oil of lavender). A mild but sustained antiseptic action can be achieved by incorporating salicylic acid (2·5 per cent) or boric acid (25 per cent) or the fungicide zinc undecenoate (10 per cent). There is a useful selection of dusting powders listed in the BPC.

**STARCH** is a polysaccharide obtained from the grains of wheat, rice or maize; it is also available in the potato. The product is described as rice starch, maize starch (corn starch), potato starch etc., according to its source. Finely powdered starch is smooth and bland to the skin. It has the important property of taking up moisture, and the insensible perspiration is readily absorbed when the skin is dusted with suitable starch powder. Starch is therefore a common and important ingredient of dusting powders—used to keep the skin dry. If sweating is profuse the excess of moisture causes starch to gel and this is obviously undesirable in a dusting powder. The gelling property can be eliminated by treating starch with formaldehyde. This treatment does not interfere with the useful physical properties of starch as a dusting powder and lubricant. Modified starch powders can be sterilised in the autoclave and are widely used to dust the rubber gloves worn at surgical operations. For this purpose they are preferred to talc because when silicates are introduced into wounds the particles behave as foreign bodies and stimulate the formation of granulomata; starch granules, on the other hand, are absorbed and excite no local reaction in the tissues.

Under favourable conditions, starch has the curious property of taking up relatively large volumes of water to form a *mucilage* and this has many practical applications. When powdered starch, thoroughly mixed with a little cold water, is suddenly raised to a high temperature with boiling water and stirred, the starch granules break down. The starch and water then form a mucilage. The consistence of this mucilage on cooling depends on the relative quantities of starch and water: a thin mucilage can be poured and is suitable for application to a mucous membrane — for example as a soothing and protective dressing to an inflamed intestinal mucosa (starch enema). Again, the starch/water combination may have the consistence of soft porridge: in this form it is spread on lint and applied as a cold poultice; thus starch provides a means of keeping the superficial tissues in contact with *water*, and this is sometimes desirable for cooling and soothing the tissues, as well as for softening crusts on the skin prior to their removal.

It is instructive to note the relationship between the therapeutic applications of starch and its common domestic use. In laundering, starch is valuable for stiffening fabrics (though substances other than starch are now widely used). A thin mucilage is employed, and in this state the starch gains access to the interstices of the material. The water of the mucilage is then driven off by means of heat (ironing), and the fabric becomes stiff from impregnation with the film of starch remaining *in situ*. Thus water is a vehicle by which starch is conveyed to fabric. On the other hand, therapeutically starch provides a means of conveying water to an epithelial surface.

The physical condition of a mucilage of starch can also be destroyed by anything which acts as a dehydrating agent. Alcohol and strong acids are therefore among the substances that are incompatible with starch mucilage. When iodine is added to starch mucilage the iodine is fixed with the formation of a blue compound called starch iodide. This reaction is utilised therapeutically: in iodine poisoning starch mucilage is given by mouth as an antidote, but the starch-iodide compound must be removed by gastric lavage, for if the compound passes into the intestine the iodine will be released and absorbed.

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CHALK is native calcium carbonate purified by elutriation. As it is amorphous and can be prepared as a smooth fine powder it may be used in dusting powders; calcium carbonate, which is microcrystalline, is less suitable for this purpose but is appropriately used in tooth-paste and in powdered dentifrice. Sifted chalk by its physical effect on the skin is protective, soothing and drying. Chalk is almost insoluble, and if sweating is profuse the powder is apt to "cake" in the folds of skin, and therefore starch, zinc oxide and talc are to be preferred for external use. Chalk is also taken by mouth when its "protective" effect on the mucosa of the alimentary canal is desired. This is a form of treatment that is largely empirical and awaiting critical assessment. When drinking water is very "hard" on account of a high content of calcium salts it is apt to cause constipation—especially in people who are accustomed to "soft" water. The action of calcium here is the characteristic one—production of quiescence in involuntary muscle—and this is achieved by the increase in the quantity of calcium salts and soaps in the intestinal contents. The medicinal use of chalk in doses of 2-4 G. every few hours represents a therapeutic application of this knowledge. It seems unlikely that the "protective" action of chalk in the bowel is similar to that of sifted chalk applied to the skin as a dusting powder. When chalk is swallowed, some of it must react with the hydrochloric acid of the gastric juice; but the calcium chloride which enters the bowel is partly converted to carbonate and bicarbonate of calcium in the upper intestine; and if large doses of chalk are given, much of it passes beyond the pylorus unchanged. In clinical practice chalk is rarely given alone when the aim is to produce intestinal quiescence: the effect is usually reinforced by adding to the mixture preparations which contain morphine and tannic acid. The value of the individual drugs used is therefore left in doubt. The reaction between chalk and hydrochloric acid creates therapeutic possibilities in relieving the gastric symptoms associated with hyperchlorhydria. The crystalline preparation, calcium carbonate, is preferred for this purpose; in this form it can be more readily compounded with other salts such as heavy magnesium oxide and sodium bicarbonate. It must be emphasised that the use of chalk or calcium carbonate *alone* as a gastric antacid is often

unsatisfactory because it causes troublesome constipation. This difficulty can be overcome by means of a judicious combination of calcium carbonate and magnesium oxide, as the magnesium salt has a laxative action.

Calcium carbonate can be used as a *diluent* or *vehicle* to provide a dose of convenient bulk when minute quantities of powerful drugs are dispensed in the form of a powder, but lactose is usually preferred.

**ZINC OXIDE.** The pharmaceutical product is a fine white powder. Its smoothness and insolubility warrant its inclusion in dusting powders, and in other preparations in common use for the treatment of skin diseases. Although soluble salts of zinc, such as zinc sulphate, can be used as astringents (p. 423), zinc oxide cannot act in this way because it is insoluble in water; it is sometimes credited with a "mildly astringent" action, but this refers to the drying effect of a powder so fine that it penetrates into every fold and crease of the skin.

The usefulness of zinc oxide is indicated by its inclusion in a large range of dermatological preparations listed in the BP, BPC, and BNF—dusting powders, lotions, creams, ointments, pastes, and gelatins. A few of these are mentioned in Appendix II. When zinc oxide is left exposed to the air it takes up moisture and carbon dioxide, and the zinc carbonate thus formed spoils the preparation. Zinc oxide is no longer given internally as there is no evidence that it has therapeutic value. Further, the salt reacts with the gastric hydrochloric acid and the corrosive zinc chloride is formed; in large doses zinc oxide therefore produces severe gastric irritation with nausea and vomiting.

**PURIFIED TALC** (Purified French Chalk). Purified Talc is purified native magnesium silicate "corresponding approximately to the formula  $Mg_6(Si_2O_5)_4(OH)_4$ ." (BPC). It may contain traces of aluminium silicate. Talc is a very fine smooth powder and it produces a characteristic soapy feeling when rubbed between the fingers. It is a common ingredient in dusting powders, and is of particular value as a dry lubricant which reduces friction between opposing skin surfaces (neck, axilla, groin, buttocks, etc.).

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OLIVE OIL is the oil expressed from the ripe fruit of *Olea europæa* which is a small tree cultivated in Mediterranean countries and elsewhere. It is pale-yellow or greenish-yellow and has a faint odour and taste. Olive oil is a mixture of liquid oils and solid oils and when cooled to 10° C. the solids precipitate and give the oil a pasty consistence.

In some parts of the world olive oil is an important foodstuff. Pharmaceutically it is used in the preparation of liniments, ointments, soaps and plasters; it has been used also to suspend insoluble drugs intended for intramuscular injection. Applied externally and gently rubbed into the skin it makes the superficial tissues softer and more pliable. In skin diseases where the lesions develop crusts of dried secretion and debris, olive oil can be used to soften the crusts: the oil is allowed to soak into them overnight and the crusts are then readily removed. Olive oil can be used as a lubricant during massage, but in general a preparation of *talc* is preferred because the powder fulfills the usual requirements and is dry and odourless. Formerly olive oil (or similar vegetable oils such as peanut oil) was in demand for making a variety of liniments (*applied* to the skin) and embrocations (*rubbed* on the skin) to produce the effects of fomentation, not by heat but by mild chemical irritants such as camphor, methyl salicylate and essential oils (oil of turpentine, etc.) and acetic acid. Here the oil serves a purely pharmaceutical purpose. If the irritant substance in the oil is strong enough to cause appreciable pain in the superficial tissues, it may relieve deep-seated pain—for example in peri-articular structures in rheumatoid arthritis. The tendency of these irritants to cause flushing of the skin by local reflex action (rube-facient action) is noteworthy but the phenomenon is not significant therapeutically; even when the cutaneous congestion is intense—as it is following inunction of esters of nicotinic acid—if it is painless the effect is merely spectacular and lacks counter-irritant value.

The soothing effect of a bland oil on superficial tissues is also apparent when olive oil is used in special circumstances in the eye, the mouth, œsophagus and stomach; and when it is used as an enema. It is not a specific remedy but may be used symptomatically to alleviate the discomfort of irritation from various causes.

In doses of two tablespoonfuls olive oil inhibits the secretion of gastric hydrochloric acid and may be used to supplement therapy of the conventional kind in cases of peptic ulcer. People who are not accustomed to take oil as such usually decline this treatment because they find it nauseating. The oil can then be emulsified to make it more palatable, but in this form it is probably rather less effective in acting as a protective and in inhibiting gastric secretion. In the management of chronic constipation where there is distension of the rectum with hard faecal masses, about 300 ml. of olive oil may be run into the lower bowel and left overnight to soften the scybala; this facilitates evacuation of the lower bowel by means of a simple enema, using several pints of warm water for the purpose. Olive oil may also be used as a vehicle for the rectal administration of drugs such as paraldehyde or ether.

Other vegetable oils which may be used as alternatives to olive oil are arachis oil (groundnut or peanut oil), sesame oil, cotton-seed oil, linseed oil, almond oil (not to be confused with the volatile oil of bitter almonds, which is mainly benzaldehyde), and ethyl oleate. Oleic acid is a straw-coloured liquid which has a faintly rancid odour. It penetrates the skin more readily than fixed oils or fats; it is therefore used—though rarely nowadays—as a solvent and vehicle for active drugs such as alkaloids and metallic oleates administered by inunction.

SOAPS are the alkaline esters of fatty acids. When caustic soda reacts with stearic acid (or with animal fat which is largely stearin) sodium stearate (Animal Soap or Curd Soap) is formed. Similarly Hard Soap or Castile Soap, which is sodium oleate, is prepared by heating the appropriate oil or fatty acid with sodium hydroxide; and Soft Soap is made in the same way, using potassium hydroxide. The soaps are sparingly soluble in cold water (animal soap is almost insoluble), but they dissolve in hot water and also in alcohol and ether; the Spirit of Soap which is so widely used for surgical cleansing of the skin is alcohol (90 per cent strength) containing 65 per cent of soft soap.

Soaps are cleansing agents. In the process of washing the skin, a lather is formed and the film of sebaceous secretion is emulsified and dispersed. Particles of dust are thus exposed and with the

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topmost layers of the stratum corneum they are dislodged by the scouring effect of gentle friction. The soaps used as *toilet preparations* are the hard Castile soaps: they are made of the finest oils and fats which have been previously deodorised and de-colourised. Shaving soaps are similar to toilet soaps but they contain added fat ("superfatted soaps") and a little alkali—which helps to soften the beard before shaving; and a shaving cream is a soap of similar type, the consistence having been modified by the addition of glycerin and water and a little vegetable oil.

SOFT SOAP is a particularly valuable detergent in the treatment of skin diseases in which it is necessary to remove scales and crusts. In the preparation Spirit of Soap, soft soap is useful for general surgical purposes and for cleansing the scalp as a preliminary to applying antiseptic lotions. When soap is included in enemas, soft soap is a convenient preparation to use (30 G. to 600 ml.): it acts as an irritant to the mucosa of the rectum and pelvic colon and thus excites peristalsis, and the lubricating action of the soap solution facilitates the passage of scybala through the anal canal. It is doubtful whether the addition of an irritant soap is necessary in enemata: the physical action of a bulky enema of warm water usually suffices to promote evacuation of the lower bowel, and if a lubricating action is desired this can be achieved equally well by means of a bland toilet soap. The excessive alkalinity of soft soap sometimes causes a mild inflammatory reaction in the rectal mucosa—with discomfort lasting for an hour or two. The irritant action of soft soap is utilised in the preparation Liniment of Soap in which the soap solution is used to emulsify camphor and an essential oil (Oil of Rosemary). Animal soap (curd soap) is so hard ("horny") that its use is reserved for pharmaceutical purposes; it is a convenient and harmless material to create the correct consistence in pills and plasters.

Soaps are not the only substances which have wetting and detergent properties. Alkaline salts and also a sulphonated preparation of castor oil have been used in industry for more than fifty years. These in turn have been displaced by numerous synthetic compounds in the past few decades. They fall into three classes: (a)



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*Anionics*—the sulphonated fatty alcohols (lauryl, stearyl, cetyl, etc.) which provide the common soapless detergents familiar from their domestic uses as shampoos and washing powders. (b) *Cationics*—quatarnary salts such as cetyldimethylbenzyl ammonium bromide, cetylpyridium chloride, cetylpyridium bromide, etc. Although they can be used as detergents, they are primarily important as antiseptics. (c) *Non-ionics*—these are polyethylene derivatives and are available as liquids or solids. In the molecule two parts can be identified with distinct physical properties and functions: one is hydrophilic; and the other is lipophilic—derived from alcohols, thio-alcohols, alkyl-phenols, or the esters of sorbitan. The non-ionic detergents are neutral and they mix with hard water and even with sea-water; they are almost foamless and are relatively ineffective in removing sebaceous secretion from the skin; their main use is as adjuvants to increase the detergent action of some of the non-ionic detergents, and they are important because they ensure success in the washing of fabric no matter what may be the quality of the water.

LIQUID PARAFFIN is classed as mineral oil—in contradistinction to the vegetable oils and the volatile or essential oils. It is a transparent, colourless liquid, odourless and tasteless. Liquid Paraffin is chiefly used as a laxative (p. 415).

HARD PARAFFIN is a mixture of solid hydrocarbons. At room temperature it is a wax-like substance; it melts at 50–57° C. Hard paraffin is incorporated into ointments in order to give them a firmer consistence when this is desirable. Hard paraffin is used also for the “wax bath” treatment of rheumatoid arthritis affecting the hands and feet. The extremities are immersed in the melted hard paraffin which is maintained at a temperature which ensures a sustained rubefacient effect. When the extremities are withdrawn from the baths the paraffin solidifies in sheaths on the skin and may be left *in situ* for an hour or two as a protective splint.

SOFT PARAFFIN is a well-known domestic remedy under the proprietary name of “Vaseline”. It is a yellow, soft, unctuous mass consisting of semisolid hydrocarbons. Soft paraffin is one of the standard ointment bases; it may be used alone or mixed with hard paraffin or beeswax to make it firmer; or with lard or a little olive

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oil to make the ointment base softer and more diffusible. The paraffins do not penetrate into the skin to any important extent, hence as ointment bases they are particularly suitable for drugs which are intended to act only on the surface. Nevertheless enough is taken up by the superficial layers of the skin to make Soft Paraffin a very reliable domestic remedy for the treatment of chapped hands and superficial irritation. They are mineral substances obtained from petroleum and shale, and they therefore do not become rancid—a distinct advantage by comparison with certain vegetable oils and animal fats. White Soft Paraffin is the bleached preparation of Yellow Soft Paraffin.

GELATIN is a protein extracted from collagenous material. It is available in translucent, almost colourless, sheets or shreds. If gelatin is steeped in cold water it becomes soft and swollen, imbibing 5 to 10 times its weight of water; it is soluble in hot water and forms a gel on cooling. Gelatin suitably prepared is soluble in mixtures of glycerin and water, but it is insoluble in strong alcohol.

Gelatin is important pharmaceutically, especially in compounding preparations for application to the skin: a paste of gelatin (18 per cent) in equal parts of glycerin and water forms an excellent protective, and a basis in which to incorporate antiseptics such as Ichthyol (Ichthammol), Resorcin, or soothing preparations such as Zinc Oxide (Gelatin of Zinc or Unna's Paste). Another pharmaceutical application of gelatin is seen in the manufacture of gelatin capsules. These are thin-walled cylindrical containers, about 10 mm.  $\times$  5 mm. which are used as a means of administering drugs which would otherwise be unpleasant to take. Plain gelatin capsules dissolve in the stomach and release their contents in a few minutes. If it is desired to delay the digestion of the capsule it can be made resistant to the gastric juice by treating it with stearic acid or keratin solution or by hardening it in formalin. The demulcent action of gelatin is illustrated by its wide use as sweets ("gums") or as pastilles—medicated and flavoured for their effects in the mouth and throat. Such preparations are compounded from gelatin (12 per cent), glycerin (50 per cent) and water; suppositories and bougies can be prepared in similar

fashion, the appropriate consistence being achieved by adjusting the gelatin content. Manufacturers have revealed much ingenuity in presenting gelatin as a nutritious foodstuff in various appetising forms suitably flavoured.

GLYCERIN or glycerol is a trihydric alcohol  $C_3H_5(OH)_3$ , obtained by hydrolysis of fats and fixed oils. It is a clear syrupy liquid miscible with water and with ethyl alcohol. Glycerin has a sweet taste followed by a sensation of warmth. It is the *hygroscopic effect* of pure glycerin that accounts for some of its therapeutic uses. If undiluted glycerin is smeared on an abrasion of the skin it causes stinging pain because of the sudden dehydrating action on the superficial cells—including sensory nerve endings. When glycerin has been diluted with water and its physical affinity for water thus satisfied, it ceases to be hygroscopic. If an aqueous preparation be applied to the skin, when the water evaporates a film of hydrated glycerin remains: this is the objective when glycerin is used in a hand lotion. Water is an essential vehicle for conveying glycerin to the skin: the glycerin does not evaporate but remains as a film on the epidermis and by its emollient and protective effects it accelerates the rate of healing of minor abrasions (for example, chapped hands). The irritant action of undiluted glycerin is seen also when it is introduced into the rectum—either by means of a suitable syringe, or as suppositories of glycerin compounded with gelatin. The glycerin, by the purely physical effect described above, produces irritation of the rectal mucosa and this stimulus sets up peristalsis in the pelvic colon and descending colon. Failure is usually attributable to giving too small a dose of glycerin (not less than 30 ml. should be given) or to the dispersal of the glycerin in faecal matter in the rectum. When evacuation of scybala begins, their passage through the anal canal is eased by the lubricant action of the layer of glycerin; but the student must be clear that the principal effect of undiluted glycerin is *irritation*, and in the absence of this, glycerin suppositories and the glycerin “enema” would be valueless as evacuants. It follows that glycerin given by mouth is *not* a laxative because its hygroscopic effect is rapidly expended when it mixes with the contents of the stomach.

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Acetphenolisatin and related compounds are synthetic preparations which have laxative properties when given orally, and they can also be used in the form of suppositories as an alternative to glycerin. They include "Cirotyl", "Dulcolax" and "Vcripaque".

Glycerin is widely used in hand lotions (see above): its emollient and protective actions are valuable in themselves; and in lotions that contain insoluble salts such as calamine (native zinc carbonate) glycerin helps to suspend and disperse the solid particles. The physical properties of glycerin account for its inclusion in gelatin pastilles used as demulcents in the mouth and throat.

It is also used as a solvent for producing various effects *locally*: a mild antiseptic action can be obtained from Glycerin of Borax (sodium borate) and Compound Glycerin of Thymol—both commonly used in oral hygiene; glycerin of alum and Glycerin of Lead Subacetate are mild astringents; and glycerin of phenol was formerly used—not as an antiseptic, but for the slight anæsthesia produced by the released phenol. The therapeutic applications of the medicated glycerins are necessarily limited by the potentially irritant effect of the undiluted glycerin: for example, they must not be instilled into the eye; and the addition of water to dilute glycerin of phenol causes the release of phenol in high concentration (this preparation is therefore diluted with more glycerin).

Glycerin has also been used compounded as a paste with exsiccated magnesium sulphate for application to discharging boils and carbuncles. Here again the underlying principle is concerned with dehydration: both the glycerin and the dry magnesium sulphate attract fluid out of the superficial tissues and promote loosening and separation of inspissated pus and debris; when the surface has been cleansed in this way bland dressings can be applied to the granulation tissue to encourage spontaneous healing. This kind of treatment is now seen less frequently because infection of superficial tissues can usually be aborted by specific antimicrobial therapy. Pure glycerin may be run into the uterine cavity to exert a lymphagogue effect by dehydrating the mucosa: this promotes the evacuation of infected secretion in chronic endometritis. This procedure, however, must be regarded as a mere ancillary to specific therapy.

A combination of glycerin (for its hygroscopic effects) and ichthyl (as a mild antiseptic) is available for application to the cervix uteri. A similar preparation is often used empirically to relieve the

sense of congestion and irritation in an œdematous limb (usually the leg) in the early stages of thrombophlebitis.

Glycerin has many applications in commerce: it is often used to improve the physical consistence of pharmaceutical and cosmetic preparations, and it can be employed as a preservative and a sweetening agent.

LARD is the purified internal fat of the hog. At room temperature (about 18° C.) lard is a white unctuous fat with a faint smell. It may go rancid, but this can be prevented by the addition of benzoin (2 per cent). Lard is a valuable emollient and is included in many compound ointment bases. It melts at body temperature and therefore diffuses over a wide area when applied to the skin. Lard passes fairly readily through the epidermis and thus inunction of ointments which contain lard may lead to the absorption of significant quantities of drugs. This method of administration of active drugs is practically obsolete, but it is still necessary to avoid adding alkaloidal bases to lard in case excessive absorption should occur after inunction with the development of constitutional toxic effects.

WOOL FAT (Anhydrous Lanolin) is the purified fat of sheep's wool, freed from water. Wool fat as such is far too tenacious for use as an ointment. However, it has the peculiar property of taking up water to form a water-in-oil emulsion: this is Hydrous Wool Fat or Lanolin and it contains 30 per cent of water. Even so, lanolin is not a very satisfactory ointment base as it retains some of the stickiness of wool fat, but lanolin can be usefully compounded with other fats and oils. On account of its water content lanolin is an excellent vehicle for water-soluble drugs, and it can be used for the preparation of cold creams—though Emulsifying Wax and Wool Alcohols (see below) are now more commonly used to make elegant preparations of this type. Simple Ointment is principally soft paraffin with a little hard paraffin and wool fat added. It is also suitable for making water-in-oil emollient creams. *Wool alcohols* are obtained by saponification of the grease in sheep's wool and then separating the fraction that contains

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cholesterol and other alcohols: it is a mixture of steroid alcohol and triterpene alcohol; when cold it is a golden-brown, brittle solid, but is plastic when warm. Wool alcohols take up 50 per cent of water to form Hydrous Ointment—a useful cold cream for emollient, protective and cosmetic purposes. Like hydrous wool fat, wool alcohols (as hydrous ointment) can be used as a vehicle for the *inunction* of certain drugs. Water-in-oil emulsions are more valuable for incorporating fat-soluble drugs such as menthol, camphor and volatile oils, and as emollient skin protectives, than oil-in-water emulsions; but wool alcohols (2·5 per cent) may be added to oil-in-water emulsions to make them more effective as emollients.

CETOSTEARYL ALCOHOL (also called Lanette Wax), is a cream-coloured unctuous mass, insoluble in water. It is a mixture of solid aliphatic alcohols, chiefly stearyl and cetyl alcohols obtained by reduction of stearic or palmitic acids or from sperm oils. *Sodium Lauryl Sulphate* is a mixture of sodium normal primary alkyl sulphates, chiefly sodium lauryl sulphate: it is a white or pale-yellow powder, soluble in water (1 in 10) to form an opalescent solution. Cetostearyl alcohol is used with sodium lauryl sulphate to prepare Emulsifying Wax which forms oil-in-water emulsions readily with water to serve as cosmetic creams, or with paraffins or fixed oils (see above) to serve as ointments. These creams or ointments mix promptly with the skin secretions and are absorbed without leaving a greasy surface; and into these preparations may be incorporated water-soluble drugs which are thus more effectively absorbed than from water-in-oil emulsions. They are also useful skin protectives in industry where greasy materials are handled. Sodium lauryl sulphate lowers surface tension and is a detergent or cleansing agent, effective even with hard water. It is, being anionic, also a non-irritant antiseptic against Gram-negative organisms and solutions are used in surgery to cleanse the skin (see also Soaps p. 608). Cetostearyl alcohol and sodium lauryl sulphate are compounded to make Emulsifying Wax, and this in turn is incorporated into soft paraffin in making Emulsifying Ointment—which may be modified to form Hydrous Emulsifying Ointment, containing nearly 70 per cent of water.

## DILLING'S CLINICAL PHARMACOLOGY

The emulsifying ointments are widely used as bases for cosmetics and for dermatological remedies (see BPC).

BEESWAX may be melted and worked into other ointment bases in order to alter their consistence. If given internally, beeswax is not absorbed.

OIL OF THEOBROMA (Cocoa Butter) is a solid fat, light yellow in colour, expressed from the roasted seeds of *Theobroma cacao*. It melts at a temperature somewhat below that of the body. Although it is a standard preparation for making suppositories, it has also been used for lip salves, bougies and pessaries—which offer convenient ways of delivering a drug to a restricted part of the body—sometimes to produce a local action and at other times because this route of administration offers advantages over others.

PYROXYLIN (Dinitrocellulose) consists of white malted filaments like cotton wool. It is highly inflammable. Only one preparation is of pharmaceutical importance—Flexible Collodion. This is made by dissolving pyroxylin in a mixture of alcohol and solvent ether; a little resin and castor oil are added. Collodion is painted on the skin (for example, over an incision) and when the ether has evaporated the lesion is covered with a pellicle of pyroxylin and resin; the castor oil makes this new “skin” flexible. It is often an advantage to place a thin wisp of cotton-wool over the part and paint this with collodion.

DEPILATORY PREPARATIONS. The active constituent is Barium Sulphide. It is usually available as a powder mixed with starch, French chalk and powdered soap—to which a trace of perfume may be added. When required for use, a little water is added to the powder and the preparation is thus made into a cream. This is applied to the skin and left for five minutes. It is then removed by gently scraping the surface with a spatula or a blunt knife. Barium sulphide has a destructive effect on hair. After exposure for a few minutes the hair shafts become swollen and deformed—often assuming a corkscrew appearance; and at

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this stage can be readily scraped off the epidermis. If preparations containing barium sulphide are left in contact with the skin for more than five minutes they often cause local irritation and erythema which may last an hour or two.

**SALTS OF HEAVY METALS.** Soluble salts of heavy metals such as Lead Acetate, Zinc Sulphate and Silver Nitrate produce astringent or corrosive effects on surface epithelium according to the circumstances in which they are employed. These actions are of limited significance in modern therapeutics. The general principles governing their use are considered elsewhere (p. 579).

## INSECTICIDES

Insecticides kill the mature insect. Some of these compounds attack the organism at an earlier stage of its development, for example, larvicides. The chemical compounds used are mostly synthetic, and they are of considerable medical importance because they may also cause poisoning in man and in animals. The circumstances in which they are employed in the field increase the danger: insecticide sprays and dusts may cause heavy contamination of the air (inhalation) and of the clothing (dermatitis and percutaneous absorption).

Insecticides have become extremely important in the practice of preventive medicine because they can be used to kill the vectors of certain diseases: these include mosquitoes (malaria and yellow fever), sandflies (sandfly fever), lice, mites, and ticks (the typhus group of diseases). Details regarding the use of insecticides in the practice of public health are available in textbooks of hygiene and tropical medicine. In temperate climates the main causes of human infestation are fleas, lice and the itch mite of scabies. The common house-fly is a carrier of dysentery; and (especially in rural areas) the midge and the horse-fly cause much inconvenience and also physical disabilities of varying severity.

**DICOPHANE** (DDT; Dichloro-diphenyl-trichloroethane) is important both as an insecticide and as a parasiticide. It is a white crystalline powder with a faint aromatic odour; almost insoluble



in water but moderately soluble in vegetable oils, kerosene, and various organic solvents. When used as a powder it is diluted to 10 per cent strength with powdered talc or kaolin; it may also be conveniently used as a spray made up in suitable solvents. In low concentrations it is lethal to mosquitoes, house-flies, lice, and to many other insects and arthropods. Dicophane is effective only when it comes into direct contact with the body of the insect; it is absorbed through the cuticle or by contamination of the insect's legs. It has a powerful depressant effect on the nervous system and kills the insect by causing complete paralysis.

*Toxic Effects.* When used with reasonable care, dicophane is not likely to cause toxic disturbances in man. Such effects have however been reported following ingestion, extensive contamination of the skin, or prolonged inhalation. In animals and in man it may cause tremors and even convulsions. In cases of chronic poisoning the drug affects the cerebral cortex and the cerebellum. One of the immediate dangers in acute poisoning is the action of dicophane in sensitising the myocardium to the action of adrenaline—an effect it shares with many other chlorinated hydrocarbons. In man the toxic effects are similar. There is no specific antidote for dicophane poisoning; treatment is on symptomatic lines. If the drug has been swallowed, the stomach should be washed out gently. A large dose of magnesium sulphate (a tablespoonful in half a tumbler of hot water) should then be given followed by at least two tumblerfuls of sweetened fruit juice; milk, fats and oils are strictly contra-indicated as they hasten absorption of the poison.

*Absorption, Fate and Excretion.* After ingestion a large proportion is excreted in the faeces; relatively little is absorbed. In the powdered form dicophane does not pass through the skin, but penetration does occur when the drug is applied in organic solvents. Absorption by the respiratory tract is a real danger when dicophane is used in the form of an aerosol spray or when the atmosphere in a room is heavily charged with dicophane dust.

In the body dicophane tends to concentrate in the fatty tissues. It is broken down to dichlorodiphenyl acetic acid and other un-

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identified degradation products. Some of these appear in the urine, and elimination proceeds slowly for about 10 days.

**THERAPEUTIC USES.** Dicophane was successfully used during the Second World War to combat an epidemic of typhus fever in Naples and elsewhere. At Army centres in the city a high proportion of the population received the powder (10 per cent in talc) as an insufflation into their clothing. The effectiveness of dicophane has been repeatedly confirmed as a means of terminating epidemic diseases spread by insect vectors. Clothing can be impregnated with dicophane solution (1·2 per cent) to ensure freedom from infestation by lice and fleas. The number of mosquitoes in an area can be very greatly reduced by the use of dicophane as a dust or spray over the breeding grounds: about 1 G. per sq. m. suffices for a period of 4-6 weeks.

For treating the head when it is infested by lice, the Application of Dicophane (30 ml. of a 2 per cent suspension) is rubbed into the hair, and the head is then swathed in a towel for 24 hours. It is often necessary to repeat this treatment weekly for three weeks. Newly hatched larvæ are killed in this way, though the eggs (nits) are unaffected by dicophane. The main disadvantage of dicophane as an insecticide for horticultural purposes is that its action is slow in onset. Pyrethrum powder is therefore sometimes added to dicophane in order to ensure an immediate insecticidal effect. There is also some evidence that dicophane-resistant strains of mosquitoes and body lice are emerging.

**GAMMA BENZENE HEXACHLORIDE** (Gamma BHC) is a white powder with a rather objectionable odour, insoluble in water, but soluble in organic solvents. It is particularly the gamma isomer of hexachlorocyclohexane that is highly insecticidal. Like dicophane it is absorbed by insects on contact, but its action is immediate and more powerful. Lice, fleas, and ticks are susceptible to concentrations of 0·01 per cent or less. Dusts and sprays are used. Sprays of 0·1-0·5 per cent in kerosene are effective for house-flies but being more volatile than dicophane it does not persist so long. Some resistant strains have been reported.

Gamma benzene hexachloride is very active against head-lice

when it is applied as a 0.2 per cent alcoholic solution, or as a 0.1 per cent suspension in Gamma Benzene Application. About 30 ml. is rubbed into the hair and left for twenty-four hours. It is also successful in scabies as a 1 per cent emulsion, applied for twenty-four hours as a thin film over the whole body.

*Toxic Effects.* It is safe to apply Gamma BHC externally to patients, but dusts may irritate the nasopharynx. It does not readily penetrate the alimentary canal, but if it is absorbed it is particularly toxic to the central nervous system, and may cause convulsions. There is no specific treatment; symptomatic measures are indicated.

**OTHER CHLORINATED INSECTICIDES.** Chlordane, Aldrin and Dieldrin have been synthesised more recently. They are more powerful than dicophane, and their effect is more prolonged than that of Gamma BHC. Although too toxic for clinical use against parasites, they are valuable insecticides in pest control. Toxic effects and treatment are similar to those described for dicophane.

*Organophosphorus Compounds.* Several compounds of this type are used to control the occurrence of various pests in agriculture and horticulture, but they are too toxic to man to be used clinically as insecticides. Even in small quantities they are highly dangerous, and special regulations have been passed to protect workers who handle them. Their actions are essentially those of powerful parasympathomimetic agents like di-isopropylfluorophosphate (DFP) mentioned on p. 118.

Examples (in ascending order of potency as anticholinesterases) are octamethylpyrophosphoramidate (OMPA)—which is about as powerful as Dyflos but lacks the effect of this compound as a stimulant of the central nervous system-tetraethylpyrophosphate (TEPP), and hexaethyltetraphosphate (HEET). They are cholinesterase inhibitors, and they have a prolonged and cumulative effect. Accidental poisoning may occur from inhalation or ingestion, or the compound may penetrate the intact skin. A man may die within an hour of exposure to these compounds. Their effects in man can be anticipated from their parasymp-

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pathomimetic action: there is accumulation of acetylcholine in the tissues, causing increased activity of smooth muscle and secretory glands, bradycardia, muscular twitching, weakness, respiratory distress, and convulsions. Atropine counteracts the central and muscarinic effects, but it does not affect the muscular weakness. Atropine must be given early, 2 mg. intravenously, and 1-2 mg. repeated hourly until the pupils dilate; up to 20 mg. may be needed in a day. Signs of respiratory failure call for oxygen therapy and artificial respiration. As pyridine-2-aldoxime (2-PAM) and diacetyl monoxime (DAM) have been shown to reverse the state of cholinesterase inhibition produced in man by these compounds, they may be given *in addition to atropine* to relieve non-muscarinic actions. When the skin has been contaminated by organophosphorus compounds it should be thoroughly washed; in addition to the use of soap, washing soda or baking soda should be added to the washing water to make it strongly alkaline. If organophosphorus compounds are swallowed, the stomach should be washed out with a sodium bicarbonate solution.

Workers handling these insecticides should wear protective clothing, masks, hats, and rubber gloves, and wash themselves thoroughly when the job is finished.

*Dinitroresols* (DNC) have a use in agriculture and horticulture as insecticides and weed killers. Their main toxic action in man is that of increasing cellular metabolism. At one time they were proposed as therapeutic agents for use in combating obesity, but they were soon abandoned because of their alarming effects. Poisoning results in profuse sweating, restlessness, weakness, loss of weight, tachycardia, flushing, deep rapid respirations, and eventually respiratory and cardiac failure. Treatment is symptomatic: it is directed to the management of hyperpyrexia and correcting fluid and salt loss; the administration of oxygen, and the use of barbiturate may be necessary.

*Pyrethrum* from the dried flowerheads of *Chrysanthemum cinerariæfolium* is an insecticide included in fly sprays for domestic and horticultural use. It may be added to dicophane or gamma benzene hexachloride for its immediate action.

## DILLING'S CLINICAL PHARMACOLOGY

*Derris* from the dried rhizome and roots of species of *Derris* contains rotenone. It is a common ingredient of insecticidal preparations used by gardeners. It has also been used clinically in scabies, but it has a tendency to cause irritation.

### PARASITICIDES

BENZYL BENZOATE occurs as colourless crystals or as an oily liquid with a faint aromatic odour. It is widely used as an acaricide in scabies as Application of Benzyl Benzoate (25 per cent w/v with emulsifying wax and water). It is highly effective and of low toxicity. The emulsion is conveniently applied by means of a shaving brush: all the skin is treated below the level of the clavicles (the preparation is not applied to the face). When the skin is dry a second coat of emulsion is applied. Twenty-four hours later a bath is taken and clean underwear is put on. The treatment may be repeated several times.

Benzyl benzoate is also used with excellent results against pediculosis. After shampooing and fine combing, 30 ml. of the emulsion is rubbed into the hair daily for a week.

*Sulphur preparations.* Ointment of Sulphur (10 per cent sublimed sulphur in white simple ointment) and Mesulphen (dimethylthianthrene, 25 per cent organically combined sulphur) can be used as parasiticides for scabies and pediculosis. Their use, however, is limited as they have an objectionable smell and they tend to irritate the skin.

*Crotamiton* (N-Ethyl-N-o-tolylcrotonamide) may be used as an acaricide in 10 per cent strength as a cream or a lotion. Two or three applications at daily intervals usually suffice. Crotamiton is more often used as an antipruritic.

### INSECT REPELLENTS

DIMETHYL PHTHALATE (DMP) is a clear, faintly yellow, oily liquid, with a slight aromatic odour, soluble in water 1:250, miscible with alcohol, ether and most organic solvents. It is an effective repellent for mosquitoes, mites, ticks, fleas and midges. It is applied as a cream or lotion (not less than 35 per cent strength)

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and the effect usually lasts for about 3 hours. It may cause temporary smarting and it should not come in contact with the eyes or mucous membranes. DMP damages plastics, for example most modern spectacle frames.

DIBUTYL PHTHALATE (DBP) is a clear, almost colourless, liquid, nearly odourless, soluble in water 1:2,500, miscible with alcohol and with ether. It is a slightly less effective repellent than DMP, except against the mite vector of scrub typhus. As it is less volatile than DMP and less easily removed by washing, it is preferred for impregnating clothes.

Ethohexadiol and butopyronoxyl are useful in conjunction with DMP used as insect repellents.

## FUNGICIDES

A fungicide is a drug which is used therapeutically to kill a fungus growing on (or in) the tissues of the host.

Fungous (or fungal) infections of the skin and mucous membranes are fairly common in this country. Some are increasing in frequency because of the widespread use of antibiotics in medical and veterinary practice. Thus there has been a conspicuous increase in the number of monilial infections—and many of these are now apt to become major disabilities. Other fungous infections which are of clinical importance are *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Candida albicans*.

Some infections are more resistant than others to treatment. This may be the result of characteristics inherent in the fungus itself. More commonly it is because various circumstances make the invading organism inaccessible to treatment. For example, infection of the feet is often difficult to eradicate because the skin—especially the interdigital areas—is normally warm and moist, and in the macerated epidermis fungi thrive unless the organisms are removed by the appropriate routine of thorough washing. The insidious onset of fungous infections is apparent from the fact that *Tinea pedis* may exist on the skin of the feet for many years before it becomes clinically active. During this phase (or later) the fungus becomes established in the superficial layers of

the skin and around the nails, and in these sites it is unaffected by fungicides—however potent these may be on the surface.

Many drugs used as germicides are also effective fungicides, but some antiseptics cause too much damage to the superficial tissues of the host for the repeated application needed in fungous infections. It is necessary also to select the pharmaceutical preparation of the fungicidal drug with due regard to the state of the lesions at the time of treatment: an acute eruption with a weeping dermatitis calls for the use of a lotion, whereas dryness of the skin may justify the use of a paint, a paste or an ointment.

**IODINE** is an effective fungicide in low concentration (0.5–5 per cent of the Tincture) and its powerful bactericidal action is an added advantage when the area is secondarily infected. Repeated application may cause a local inflammatory reaction; and occasionally idiosyncrasy to iodine causes severe general reactions, fever and various skin eruptions. *Silver Nitrate* 3–5 per cent in nitrous ether may be used. The skin at the site of application develops a brownish discolouration temporarily from the formation of silver sulphide. *Magenta* is traditionally used as Castellani's Paint (Paint of Magenta). The phenol and resorcinol it contains also have fungicidal properties. *Crystal Violet* (Medicinal Gentian Violet) 0.5 per cent is frequently applied to the skin and mucous membranes for monilial infection, due to *Candida albicans*.

**SALICYLIC ACID COMPOUNDS** are preferred when fungous infections are less acute, and especially when they are in a dry scaly stage, as salicylic acid is a keratolytic agent. Whitfield's Ointment (Compound Ointment of Benzoic Acid) retains its popularity after many years. It contains benzoic acid 6 per cent, salicylic acid 3 per cent, in emulsifying ointment.

The introduction of **FATTY ACIDS** in the treatment of fungous infections has proved to be a major advance—a practical application of the observation that some of the fatty acids that occur normally in sweat inhibit the growth of fungi. Fatty acids have several desirable properties as fungicides: they inhibit or destroy a wide range of fungi; they penetrate the superficial skin; they

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are non-irritant and do not tend to promote sensitisation; and they do not destroy or stain the skin. Long-chain fatty acids are effective, whether saturated or unsaturated, and one in common use and somewhat superior to the others is *Undecenoic Acid* (Undecylenic Acid). It is an 11-carbon unsaturated compound. Like the fatty acids in general it is more effective in an acid medium. Concentrations from 2 to 15 per cent are used for tinea infections, moniliasis and mycotic vulvovaginitis—in the form of dusting-powders, ointments or emulsions according to individual needs. Concentrations up to 1 per cent are applied to mucous membranes. Higher concentrations may be irritant. *Zinc Undecenoate* when added to undecenoic acid up to 20 per cent appears to increase its efficiency—for example in Dusting-powder of Zinc Undecenoate (zinc undecenoate 10 per cent, undecenoic acid 2 per cent) and Ointment of Zinc Undecenoate (zinc undecenoate 20 per cent, undecenoic acid 5 per cent). *Octoic Acid* (Caprylic Acid) is frequently used as its salt Sodium Octoate in 5-10 per cent solutions, powders or ointments, and especially the powder or 5 per cent douche for monilial vulvovaginitis. *Propionic Acid* and Sodium Propionate are used alone or as ingredients of compound preparations, as a 2.5-3.5 per cent ointment or 0.25 per cent dusting-powder, or 10 per cent ointment or dusting-powder respectively.

The Solution (or Tincture) of Iodine, 2-5 per cent, or Whitfield's Ointment is used in association with epilation for ringworm of the scalp. *Salicylanilide* is a more specific remedy for ringworm of the scalp due to *Microsporon audouini*. It is a condensation product of salicylic acid and aniline. An ointment is used containing 4.5 per cent of the drug.

NYSTATIN ("Mycostatin"), an antibiotic from *Streptomyces noursei*, is a fungicide which is used extensively for moniliasis (p. 480).

PREVENTION OF SPREAD OF FUNGOUS INFECTION is important in communities using public swimming-baths. There is often a special hazard in the use of ablution centres and baths provided for closed communities such as residential schools,



military establishments, etc. Provision of foot baths containing 1 per cent sodium hypochlorite, or 1 per cent potassium permanganate minimises the risk of spread of infection. Alternatively fungicidal dusting-powders may be used, such as the dusting-powder of zinc undecenoate, or Compound Dusting-powder of Salicylic Acid (salicylic acid 3 per cent, boric acid 5 per cent).

### SCLEROSING AGENTS

Sclerosis literally means *the state of hardness*. A sclerosing agent is one which is deliberately used to produce in the tissues certain physical changes which are likely to be of therapeutic value; in this context these effects necessarily refer to local hardening. In practice the term "sclerosing agent" is virtually restricted to drugs which, when introduced into a vein, excite an inflammatory reaction in the endothelium, the onset of local thrombosis, and sealing of the lumen of the vessel. The process called "organisation" of the inflamed tissues usually results in permanent obliteration of the vein; it then becomes a string-like cord which feels hard to the hand on gentle palpation. This principle of obliteration of a potential space lined by endothelium may also be applied to serous sacs such as bursæ; and it was formerly a therapeutic procedure to produce adhesions between the visceral and parietal pleura.

The sclerosing agents are chemically a miscellaneous group of substances. Three pharmaceutical preparations which are used in the treatment of varicose veins and hæmorrhoids are mentioned below.

ETHANOLAMINE (2-aminoethanol) is the most satisfactory sclerosing agent for relieving the symptoms of varicose veins by injection therapy. It is combined with oleic acid as an oleate in the official preparation Injection of Ethanolamine Oleate. Up to 5 ml. of this preparation is injected (in divided doses) into the affected veins, and the treatment is repeated at intervals of 1-2 weeks until a satisfactory result is obtained. An obvious hazard in the use of sclerosing agents is that the solution may be inadvertently injected into the tissues around the vein or may leak out of the vein. This can nearly always be avoided by adhering carefully to standard techniques. An advantage of using ethanolamine is that the effects

## DRUGS ACTING LOCALLY

of extravasation are less severe than those which are sometimes seen after the use of other sclerosing agents.

MORRHUIC ACID is used in the form of a 5 per cent solution of sodium morrhuate, 5 to 10 ml. of which may be injected into the vein or sac. Severe allergic reactions occur more frequently than after ethanolamide therapy, and therefore sodium morrhuate is now less often used.

INJECTION OF QUININE AND URETHANE contains quinine hydrochloride 12.5 per cent, and urethane 6.25 per cent in Water for Injection. The urethane is included because it increases the solubility of quinine salts. This solution is a powerful irritant, and is apt to produce serious destruction of the tissues if leakage occurs from the lumen of the vein. The tissues of the vein itself react vigorously to the chemical trauma produced by quinine, and this treatment causes fairly severe pain and swelling; but the inflammation also subsides rapidly. An additional hazard with this preparation is the occasional occurrence of constitutional upsets which are among the toxic effects of quinine (p. 554).

## SPREADING AGENTS

HYALURONIDASE. The enzyme hyaluronidase is obtained from the testes and seminal fluid of mammals. When administered it has no effects other than the purely local mucolytic action. This action is produced by the depolymerisation of hyaluronic acid, a component of the intercellular cement substance. Hyaluronidase thus permits the rapid spread and subsequent absorption of substances introduced into tissue spaces.

When purified the enzyme is stable. It is available as a sterile white powder, dispensed in sealed containers. The powder is dissolved in water before use. Its activity is defined in terms of international Units: 1 mg. of the purified powder contains about 300 international Units.

Hyaluronidase can be used therapeutically in various ways. When saline is to be given parenterally by the *subcutaneous route*, hyaluronidase may be added to the solution in order to accelerate the rate of absorption. This often constitutes a real advantage in pædiatric practice, as in infants and young children intravenous infusion may be difficult or contra-indicated. Local swelling and

bruising of tissues tends to diminish more rapidly when the affected part is infiltrated with a solution of this enzyme.

The quantity of hyaluronidase used depends on the nature of the procedure to be undertaken. When fluid is being administered subcutaneously to correct dehydration, 1,000 international Units may be added to a litre of the fluid. If hyaluronidase is being given for a local effect, 100-500 Units dissolved in Water for Injection may be injected into the tissues. Injection of hyaluronidase through or into infected tissues should be avoided, as the local release of the enzyme in these circumstances may cause rapid dissemination of micro-organisms beyond the lesion.

### FIBRINOLYTIC AGENTS

**STREPTOKINASE AND STREPTODORNASE.** These enzymes are obtained from certain strains of streptococcus. Streptokinase was formerly known as fibrinolysin, since its most obvious action is the lysis of fibrin. This action is believed to be an indirect one, streptokinase being responsible for the activation of a fibrinolytic factor present in normal blood. Streptodornase is capable of converting thick, tenacious pus to a thin purulent fluid; this action is brought about by the depolymerisation of nucleoproteins which are derived from dead tissue cells and leucocytes and form a large component of purulent matter. The enzyme has no action on living cells.

These enzymes are complementary in action and are useful therapeutically as adjuncts to other forms of treatment (for example, antibiotic therapy) in the management of chronic suppurative and fibrotic lesions such as empyema. The preparation commonly used is a freeze-dried powder with a phosphate buffer, dissolved in Water for Injection before use to make a solution containing 20,000 Units of streptokinase, and 5,000 Units of streptodornase in 10 ml. Toxic febrile reactions are often recorded after the injection of this preparation into body cavities. When blood clot is sealing a bleeding point or when there are other circumstances suggesting an increased risk of secondary hæmorrhage, streptokinase-streptodornase preparations may precipitate brisk bleeding, and this treatment should therefore be avoided.

## CHAPTER 20

# DIAGNOSTIC DYES AND RADIO-OPAQUE SUBSTANCES

### DIAGNOSTIC DYES

IN addition to their diagnostic uses many dyes have therapeutic importance, especially as skin applications in the treatment of infective conditions.

FLUORESCCEIN is an orange-coloured powder which dissolves readily in water. The solution formed has a brilliant green fluorescence. When a little is instilled into the conjunctival sac it picks out any superficial tissue that has sustained damage through trauma or pathological change. Corneal ulcers and abrasions show up as brilliant green areas, while the background of normal epithelium remains unaffected by the dye. Eye Drops of Fluorescein contain 2 per cent of fluorescein in water.

CONGO RED is used by injection as an aid to the diagnosis of amyloid disease. The usefulness of the test depends on the fact that tissues undergoing amyloid degeneration have a special affinity for the dye. Thus when a large viscus such as the liver is the site of amyloid disease, it withdraws Congo Red from the circulating blood much more rapidly than does normal liver tissue.

Congo Red is a reddish powder sparingly soluble in water, and special care is taken in preparing the aqueous solution (1 per cent) needed for the test. The dose is 0.25 ml. per Kg. body weight intravenously. The plasma level of Congo Red is then estimated at intervals over a period of one hour; if after one hour the level of the dye has fallen by more than 30 per cent the circumstances point to a diagnosis of amyloid disease. Congo Red was formerly used by intravenous injection as a hæmostatic agent, but the procedure has not been proved to have therapeutic value.

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**AZOVAN BLUE** (Evans Blue) is a dye which when injected intravenously becomes firmly fixed to the plasma protein fraction, and is only slowly removed from the circulation. It can therefore be used to estimate the blood volume by colorimetric methods. A known quantity is injected into the blood stream—usually 5 ml. of a 0·5 per cent solution. After 20, 40 and 60 minutes blood samples are taken and the concentration of the dye in each blood sample is estimated. From these data and the use of standard formulæ the blood volume can be calculated (see *The Extra Pharmacopæia*, Vol. ii).

**METHYLENE BLUE** and **INDIGO CARMINE** are dyes which are excreted in the urine after intravenous injection. Formerly used as tests of renal function, these have now been superseded by the more accurate biochemical methods. Indigo Carmine, however, is still favoured for use during cystoscopic examinations. The dye is injected intravenously and can be seen when it is excreted at the ureteric orifices if renal function is good and the ureters patent. Methylene Blue is useful in the treatment of drug-induced methæmoglobinæmia (1 mg. of the dye per Kg. body weight).

**SULPHOBROMOPHTHALEIN** (Bromsulphalein or BSP) is related to phenolphthalein; like the latter substance it is excreted in the bile, and it can be used to assess the degree of hepatocellular damage in cases of liver disease. To carry out this test an intravenous injection of 5 mg. sulphobromophthalein per Kg. body weight is given. After 45 minutes the blood should have been completely cleared of the dye. There is no point in using this test when the patient is jaundiced: the raised serum-bilirubin level provides sufficient proof of impairment of hepatic excretory function. Its main value, therefore, is in the investigation of suspected chronic liver disease such as cirrhosis.

## RADIO-OPAQUE SUBSTANCES

Although many substances are opaque to X-rays, only a limited number of preparations are in common use to provide contrast media for the various standard radiological examinations.

## DIAGNOSTIC DYES AND RADIO-OPAQUE SUBSTANCES

**BARIUM SULPHATE** is a heavy white powder. As it is insoluble in water and in the secretions of the alimentary canal, ionisation does not occur when it is taken by mouth. Barium sulphate is therefore quite harmless even when taken in large quantities—such as are needed for a “barium meal” during radiological examination of the stomach. This is not so in the case of soluble salts of barium such as *barium chloride*: dissociation releases the highly poisonous barium ion, and on absorption this causes widespread paralysis usually ending fatally.

For diagnostic work barium sulphate is prepared as a suspension in water or milk (20–100 per cent) and made palatable with vanilla, chocolate, or other flavouring agent. The fluidity of the preparation varies from that of milk to that of thick porridge according to the purpose for which it is intended: the paste-like material is most useful for examining the œsophagus, whereas the very fluid preparations are needed to show up defects in mucosal surfaces. A barium sulphate suspension is also used as an enema for examination of the colon. The course of sinuses can also be demonstrated radiographically when injected with barium sulphate of cream-like consistence.

The other substances used as contrast-media in X-ray diagnosis are all *complex organic compounds containing iodine*. Some are iodised oils suitable for introduction into body spaces or wound sinuses, others are water-soluble compounds suitable for intravenous use or oral administration. Of the latter group those excreted mainly by the kidney may be used to outline the renal tract; those excreted mainly in the bile and concentrated in the gall-bladder are used in cholecystography.

Toxic effects from the use of organic iodides in radiology are fortunately uncommon, but acute idiosyncrasy occasionally causes angioneurotic œdema with a risk of laryngeal obstruction. Some of the compounds injected intravenously are prone to cause tissue necrosis and abscess formation if leakage occurs at the injection site. It is alleged that iodine compounds given in this way occasionally cause an exacerbation of a tuberculous process. The effect of iodine on the thyroid gland (p. 355) should be borne in mind; even the diagnostic use of organic iodide compounds

has been found to cause anomalous results in tracer studies with radio-active iodine, an effect which may persist for some months.

The other actions and uses of iodine and the phenomena called "iodism" and iodide idiosyncrasy are described elsewhere (p. 328).

**PREPARATIONS.** *Injection of Iodised Oil* ("Lipiodol") consists of iodised poppy seed oil, containing 40 per cent combined iodide. Iodised oil has been used mainly in radiography of the bronchial tree; about 20 ml. of the warmed oil is introduced by means of a gum-elastic catheter passed through the nose, or directly by injection through the cricothyroid membrane. Because of the risk of idiosyncrasy, it is usual to carry out a preliminary test for sensitivity with potassium iodide. A further hazard with this oily preparation is bronchopneumonia, resulting from spread of the oil to terminal bronchioles and alveoli and delay in clearing this from the lungs by coughing.

*Propyliodone* is now favoured for bronchography. This is prepared in a 50 per cent aqueous suspension, though an oily preparation is also available. Its advantages over iodised oil are the more rapid spread, and also the rapid absorption of the residue from the lung with consequent freedom from pulmonary complications.

*Diodone* is a good example of the water-soluble group of organic iodides. An aqueous solution of 35, 50 or 70 per cent may be injected intravenously, to outline the renal tract. This preparation is also used to demonstrate blood vessels (arteriography) or by retrograde injection to outline the renal pelves. Sudden, severe anaphylactic reactions have occasionally occurred with this preparation, as with other iodides, but these are rare; commonly there are minor side-effects in the form of nausea and flushing. Diodone has an advantage over many other preparations in this group in being much less irritant when injected; even subcutaneous administration is possible, preferably with the addition of the "spreading" enzyme hyaluronidase.

*Sodium Diatrizoate* is similar to diodone in its properties and uses. *Iodoxyl* is much more irritant if leakage occurs alongside the vein.

## DIAGNOSTIC DYES AND RADIO-OPAQUE SUBSTANCES

For examination of the biliary system substances which are excreted in the bile and concentrated in the gall-bladder are used. *Iodophthalein* is a typical example; it is a blue, crystalline dye administered orally in a dose of up to 5 G. about 14 hours before the X-ray examination of the gall-bladder is made.

*Pheniodol* and *Iopanoic Acid* ("Telepaque") have similar uses: the latter preparation is now widely used; it is given in a dose of 3 G. 10-15 hours before radiological examination. It is relatively free from toxic effects, and in the absence of vomiting, impaired absorption, or severe liver damage, it gives dense contrast.

*Iodipamide Methyl Glucamine* ("Biligradin") is a more recent addition to biliary contrast media, suitable for intravenous injection, and of special value when it is necessary to outline the bile-ducts, as well as the gall-bladder. The 30 per cent solution is injected in a dose of 20 ml. for this purpose; some excretion also occurs by the kidney, and this may show on the X-ray films.



## CHAPTER 21

### RADIO-ACTIVE ISOTOPES

AN element may exist in various forms which differ only in the number of neutrons contained in the nucleus of the atom. These different physical forms, known as Isotopes, are chemically indistinguishable. Some isotopes are stable, but the majority are unstable and disintegrate either into more stable forms of the same element, or into new elements. This process of disintegration is associated with radio-activity. The radiations are of three types:  $\alpha$ -rays, comprising helium particles;  $\beta$ -rays composed of electrons; and  $\gamma$ -rays which belong to the category of non-particulate "pure-wave" radiations. The  $\alpha$ - and  $\beta$ -rays have limited penetrating power;  $\gamma$ -rays on the other hand can pass through tissue with great ease.  $\alpha$ - and  $\beta$ -rays introduced into the body destroy the exposed tissues by ionisation;  $\gamma$ -rays pass through living cells but leave them undamaged.

*Research and Diagnostic Uses of Radio-isotopes.* Radio-activity can be detected and measured by suitable instruments. A great variety of substances which take part in biological activities can be "labelled" by incorporating radio-active isotopes in their chemical structure. Their qualitative and quantitative participation in the various biological mechanisms can then be investigated by "tracer" techniques. In this way, for example, the fate of ingested iodine, its uptake by the thyroid gland, its excretion by the kidney and utilisation in the production of thyroxine, can conveniently be studied. By the use of radio-active carbon many of the problems of protein biochemistry are being explored; and techniques which include the use of isotopic chromium have contributed to our knowledge of red-cell survival and to the measurement of corpuscular volume in health and disease.

*Therapeutic Uses of Radio-isotopes.* Radio-isotopes are used in therapy because of their ability to destroy tissue. The more active

## RADIO-ACTIVE ISOTOPES

a tissue the more sensitive it is to the effects of radiation. For this reason radiation techniques are of particular value in the treatment of neoplastic processes.

Although many radio-active isotopes have been tried as therapeutic agents, those of Iodine ( $^{131}\text{I}$ ) and Phosphorus ( $^{32}\text{P}$ ) have proved to be of special merit: iodine, because it is selectively concentrated in the thyroid gland, and phosphorus, because it is concentrated in blood, in bone marrow and in other tissues which make and destroy red cells.

$^{131}\text{I}$ . This isotope has an established place in the treatment of thyrotoxicosis. The dose is based on the size of the gland and ranges from 5 to 20 m.curies. The iodine (which is dispensed by the Radiochemical Centre, Amersham, as a weak solution of iodide in sodium thiosulphate) is taken as a drink through a straw. This form of treatment is quick, efficient, painless and safe. The full effect of a single dose is achieved after an interval of three months. An additional dose can be given thereafter, if necessary. Because the long-term hazards of radio-isotope therapy are uncertain, this form of treatment is at present reserved for patients over the age of 45, for those in whom operation would be specially dangerous, and for those who refuse other forms of therapy, or in whom other treatment has failed. The average cost of a course of treatment is £2 to £3.

Much larger doses, of the order of 100–250 m.curies, are necessary in the treatment of thyroid cancer, and these create special problems in the disposal of radio-active excreta.

$^{32}\text{P}$ . Radio-active phosphorus has a less definite therapeutic status. Its use in leukaemia has been disappointing and the results are no better than with standard X-irradiation procedures. It is superior to X-ray therapy in polycythaemia vera, however, although it has not displaced periodic venesection as a reliable method of treatment. A dose of 3–7 m.curies is given by intravenous injection, and may be repeated as necessary at 6-weekly intervals.  $^{32}\text{P}$  is supplied by the Radiochemical Centre, Amersham, as a sterile isotonic solution of orthophosphate buffered to pH 7.

Radio-active phosphorus is also used locally applied to skin tumours.

Other radio-active materials have been employed in a variety of ways. Radio-active gold ( $^{198}\text{Au}$ ) for example has been used as an implant or, in its colloidal form, as an instillation in the treatment of bladder cancer and in malignant disease involving pleura or peritoneum with effusions into the serous sacs.

*Isotopic Chromium* ( $^{51}\text{Cr}$ ). Isotopic chromium is a valuable diagnostic agent in the blood dyscrasias, especially hæmolytic anæmias. It can be used to "label" red cells and so estimate red-cell mass, blood volume and red-cell survival. It has no therapeutic applications.

## CHAPTER 22

# PRINCIPLES OF PRESCRIBING, DANGEROUS DRUGS ACT AND REGULATIONS AND SCHEDULES OF POISONS

**PRINCIPLES OF PRESCRIBING.** The general principles of prescription writing have been mentioned on p. 5 and in this section only a short statement summarising them is given.

The prescription is a written instruction to the pharmacist to supply drugs in a specified form for a particular patient. In general the prescription should be written in English. Simplicity and legibility are much to be desired. The doctor who resorts to polypharmacy and the "blunderbuss" type of therapy is nearly always a bad pharmacologist or a bad diagnostician—or both. The essential preliminary to writing a prescription is an accurate diagnosis and naming the specific remedy. Where there is no specific remedy it is often possible to prescribe drugs which give the patient relief of troublesome symptoms. In the experience of the individual family doctor, it is rarely necessary to prescribe drugs or preparations which are not listed in standard books of reference—BP, BPC, BNF. The most useful of these publications from the physician's viewpoint is the BPC (p. 4). The "structure" of the prescription as conventionally written has been discussed (pp. 5 to 10). More specifically the information needed by the pharmacist is set out as shown in the examples overleaf.

The significance of the different parts of the prescription is self-evident. The procedure is as elementary as that of writing a letter; and if the pharmacist is in doubt about the physician's intentions, etiquette decrees the greatest possible forbearance on both sides.

The prescription proper consists essentially of a list of ingredients and the dose of each. It is thus apparent to the pharmacist

# DILLING'S CLINICAL PHARMACOLOGY

Mr. A—— B—— (the patient's name)

**R** (Abbreviation for RECIPE (Take) addressed to Pharmacist)

<i>Sodium bicarbonate</i>	1 G.	} Ingredients
<i>Potassium citrate</i>	1 G.	
<i>Peppermint water to</i>	16 ml.	

<i>Make a Mixture</i>	} Instructions to the Pharmacist
<i>Send 16 doses</i>	
<i>Label: a tablespoonful in water as directed</i>	

X—— Y—— (Doctor's signature)  
Address

--/---/60 (Date)

Mr. A—— B——

**R**

*Aspirin 0.3 G.*  
*Send 100 tablets*  
*Label: Aspirin: Two tablets as directed*

X—— Y——  
Address

—/—/60

Mr. A—— B——

**R**

*Magnesium hydroxide 250 G.*  
*Label: a teaspoonful as directed*

X—— Y——  
Address

—/—/60

at a glance precisely how much of each drug the patient is to receive every time he takes the medicine. Naturally the pharmacist must be told how many doses of the medicine are to be dispensed. Formerly doctors ordered the ingredients not on the "single dose" principle but by "multiple dose": this imposed

## PRINCIPLES OF PRESCRIBING, DANGEROUS DRUGS ACT

on the pharmacist the need to perform an arithmetical exercise in division instead of multiplication. More important, it was also a practice which tended to encourage the use of the "stock mixture" as an easy alternative to judicious selection of drugs and doses according to the needs of the individual patient. There are, of course, occasions when drugs can be prescribed in bulk, and then the patient is usually instructed to take the preparation not in carefully measured amounts but by teaspoonfuls. This applies for example to the use of adsorbents which are taken freely to reduce the acidity of the gastric juice. In such circumstances the correct dose is that which gives relief and nothing is gained by complicating simple therapeutic procedures through insistence on pharmaceutical pedantry. Further examples of prescriptions are given in Appendix III. Under the National Health Service prescriptions are written on a form known as the "E.C.10" (Executive Council Form 10). It is set out to enable the practitioner to include the name, age (if under 14 years) and address of his patient, and the date. He then fills in the ingredients of his prescription, stating the single dose required for each ingredient; he adds briefly the instruction to the pharmacist (sometimes omitted because they are self-evident), and then directions to the patient—to be written on the label of the container; the practitioner signs the form with his usual signature. A margin on the right side of the form is left for the purpose of costing the prescription: this is done at a central department known as the Pricing Bureau. As the Practitioner's address is on the list kept by the Executive Council, there is no need for him to write it on Form E.C.10.

The practitioner who is familiar with the scope of the BPC and the BNF will normally use preparations listed in these books of reference. In this way he can give appropriate treatment and will almost automatically avoid the unnecessary use of medicines that are relatively expensive; and he will prescribe few drugs which are not of proved therapeutic value.

Under the National Health Service in this country a Standing Joint Committee on the Classification of Proprietary Preparations\* makes recommendations to the Central and Scottish Health

\* This Committee succeeded the Joint Committee on Prescribing.

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Services Councils. Many thousands of proprietary preparations have been classified by this Committee and that which preceded it; and the Committee's views have been submitted periodically to the Minister of Health and to the Secretary of State for Scotland. Reports are readily available through H.M. Stationery Office. Students who intend to practise in the United Kingdom will find it helpful to note in particular the names of preparations included in Categories "N", "O" and "H". The Committee's approach to problems in this field of medical knowledge is worthy of the attention of all who show a critical interest in pharmacology and therapeutics.\*

Over a period of about ten years no material changes have been made in the Committee's method of categorisation of proprietary preparations. Originally the categories were identified numerically. In 1958 it was decided to use letters of the alphabet instead of numbers for this purpose.

### PROPRIETARY PREPARATIONS

Proprietary preparations were initially classified in six categories by the Standing Joint Committee on the Classification of Proprietary Preparations:

- (1) New drugs of proved value not yet standard.
- (2) Proprietary brands of standard drugs, singly or in combination.
- (3) Standard preparations, and new remedies of proved value, in elegant form or vehicle.
- (4) Qualitative and/or quantitative modifications in the composition or combination of standard preparations, or new remedies of proved value, which are not accepted as therapeutically superior to preparations included either alone or in combination in the British Pharmacopœia, the British Pharmaceutical Codex or the British National Formulary.
- (5) Preparations not in the British Pharmacopœia, British Pharmaceutical Codex or British National Formulary, which in the Committee's view have not been proved of therapeutic value.
- (6) Preparations which are a combination of (4) and (5).

\* See Classification of Proprietary Preparations, H.M.S.O., 1959.

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Subsequently the designations were altered: the main results have been to achieve re-grouping and to use letters instead of numerals. The revised categorisation—and the relationship to the earlier one—is shown below:

**CATEGORY N.** New drugs of proved value which are not yet “standard”. (The term “standard” is intended to mean preparations described in the British Pharmacopœia, British Pharmaceutical Codex and British National Formulary.)

(This category replaces the old category 1.)

**CATEGORY S.** (a) All preparations whose active therapeutic constituents are identical with or modifications of those of “standard” preparations.

(b) Elegant preparations of drugs in Category N.

(c) Mixtures of drugs in Category N with drugs in Category S.

(This category replaces the old categories 2, 3 and 4.)

**CATEGORY P.** Preparations which are not “standard” for which *prima facie* evidence of therapeutic value is presented, but which the Committee cannot accept as of proved therapeutic value without further evidence, which must be provided within a period stipulated by the Committee.

(This is a new category.)

**CATEGORY O.** Preparations not “standard” which in the Committee’s view have not been proved of therapeutic value.

(This category replaces the old category 5.)

**CATEGORY H.** Preparations which are a combination of drugs in category O with those in categories N, S, or P.

(This category replaces the old category 6.)

The current position can now be summarised as follows—and this abstract may help the student to memorise the categories:

N = New drugs.

S = Standard drugs.

P = Postponed judgment.

O = Not of proved therapeutic value.

H = Heterogeneous—mixture of O with other categories.

If a practitioner’s prescribing costs are found to be conspicuously in excess of the average of those of his colleagues in neigh-



bouring practices, he may be invited by the Local Medical Committee (LMC) to offer an explanation for the difference. This procedure is a statutory duty devolving upon the LMC. Enquiry may reveal that there is full justification for the practitioner's high prescribing costs. On the other hand, it may be obvious that his prescribing costs are high because he is using expensive proprietary preparations when he might equally well prescribe standard preparations (BP, BPC, BNF) where these are available; or he might be ordering unnecessarily large amounts of drugs—and this may increase his prescribing costs even though relatively few proprietary preparations are used; again, the fault may lie in his insistence on prescribing drugs for an excessively high proportion of his patients—revealing his undue dependence on medication to reinforce suggestion. The thoughtful practitioner will take into account the fact that there are many pharmaceutical preparations which have not been proved to have therapeutic value. The practitioner reserves the right to make his own judgments, but he has nothing to gain by ignoring the opinion of independent assessors who have scrutinised the claims made on behalf of a pharmaceutical preparation.

#### THE DANGEROUS DRUGS ACT AND REGULATIONS

These concern the doctor in that they lay down, among many other regulations, certain rules for the prescription of "Dangerous Drugs". The word "dangerous" in this context means *drugs liable to cause addiction*, that is to say:

1. Opium, its alkaloids and their salts and any preparation containing not less than 0.2 per cent of anhydrous morphine or of diacetylmorphine in any quantity.
2. Coca leaves, cocaine, synthetic cocaine and any preparation containing not less than 0.1 per cent of cocaine or ecgonine.
3. Indian Hemp.
4. Pethidine.
5. Methadone.
6. Phenadoxone.

There are certain exceptions to these rules but as it is never wrong to use the format of a DDA prescription, it is more convenient to do this than to memorise exceptions.

## PRINCIPLES OF PRESCRIBING, DANGEROUS DRUGS ACT

A prescription for any of the substances referred to in the Dangerous Drugs Acts and listed above must fulfil the following requirements:

(1) The address of the doctor writing the prescription must appear on it unless the official National Health Service prescription (Form E.C.10) is used.

(2) The name and full address of the patient and the date on which the prescription is written must be plainly stated.

(3) The *total quantity* of the active agent to be dispensed must be given unless an "official" preparation (in the present context BP, BPC or BNF) is used, when the total amount of the "official" preparation asked for in the prescription must be stated.

(4) The doctor, who must be on the Medical Register, is required to sign the prescription in his own handwriting.

(5) No prescription can be dispensed more than once unless the pharmacist is given written instructions clearly stating the time that must elapse between successive dispensings. Even when this is done no prescription may be dispensed more than three times in all. This rule does not apply to prescriptions on Form E.C.10, that is under the National Health Service, as these can in any event be dispensed once only.

DETAILS OF A PRESCRIPTION FOR A DANGEROUS DRUG. (The numerals refer to the explanatory paragraphs set out above.)

(1) Doctor's Address

(2) Date of prescription

(2) Patient's name and address

**R**

Ingredients

Single dose

Vehicle (if any)

to amount of each dose

Directions to pharmacist

(3) { Total quantity of *active agent*, e.g. Morphine or of the *official preparation*, e.g. Tincture of Opium BP, in the prescription (i.e. the amount in each single dose multiplied by the number necessary to arrive at the total quantity of the *preparation* prescribed).

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Label: Instruction to patient.

- (5) { If a "private" prescription, i.e. one not written on Form E.C.10, it may be repeated on a given date and on one other given date—dispensed three times in all.

(4) Doctor's signature.

**POISONS SCHEDULES.** The Pharmacy and Poisons Act (1933) and the Poisons Rules provide for the control of the supply of poisons to the public. Appended to the Poisons Rules are sixteen Schedules. Those of most general interest are *Schedules 1 and 4*. The former describes those poisons in respect to the sale, supply and storage of which more stringent conditions must be satisfied than are required for the other poisons in the Poisons List. Among many other parts Schedule 4 is designed to prevent anyone obtaining certain listed poisonous substances, unless he presents a prescription written by a registered medical practitioner, dentist or veterinary surgeon. Schedule 4 poisons are drugs considered to have serious or fatal effects on overdosage, and the list is amended from time to time to keep it up to date. For such substances it is advisable to use the same form of prescription as for the Dangerous Drugs. In a reference book like *The Extra Pharmacopæia* a mark **S4** is placed in the margin against the name of any substance on the Schedule 4 list and a **D** against any drug listed in the Dangerous Drugs Act.

Schedule 4 poisons include preparations of the following types: antihistamines, barbiturates, phenylbutazone, sulphonamides, thiouracil and its derivatives, troxidone, amidopyrine, sulphonal and many other potentially poisonous substances.

*Precautions to be Noted in the Treatment of Children and Old People.* In this short section further attention is directed to the need to adjust the doses of drugs in accordance with the age of the patient (see also Chapter I).

**CHILDREN.** It is obviously desirable to consider dosage in relation to the patient's body weight, but even so it must be remembered that children (and especially infants) may be exces-

## PRINCIPLES OF PRESCRIBING, DANGEROUS DRUGS ACT

sively sensitive to certain drugs. This is seen in the action of CNS depressants in general and in the case of *morphine* (and kindred drugs) in particular. On the other hand, considered on the basis of body weight, children are remarkably tolerant of drugs in the *atropine* group. Several formulæ have been devised to enable the prescriber to determine the appropriate dose of a drug for a child: one of these is mentioned on p. 19. Such formulæ should not be used for children under the age of 3 years. The practitioner is well advised to be guided by a book of reference such as the BNF which includes a separate *Infants' Section*.

OLD PEOPLE appear to be very sensitive to certain drugs. *Barbiturates* should be used cautiously as they often cause excessive drowsiness: this is to be expected if there is impairment of hepatic function and failure to destroy the drug with the usual speed, or renal insufficiency and consequent slowness of excretion (phenobarbitone). Barbiturates often produce a state of mental confusion in old people: the probable explanation is that the abnormality is latent (for example on account of progressive cerebrovascular disease), and it becomes apparent for a limited time while the hypnotic effect of the drug is wearing off. Another factor which may be important occasionally is the habit—fairly common among old people—of taking an occasional nip of brandy; barbiturates and alcohol taken together may well produce profound hypnosis and subsequent mental confusion. Finally it should be noted that occasionally people in advanced old age tolerate the rapidly acting barbiturates without untoward effects. It is therefore impossible to make generalisations. Consideration must be given to the results obtained on the individual patient. Many doctors, however, prefer to use chloral hydrate as the hypnotic of choice in old people rather than risk the ill-effects that occasionally follow the use of barbiturates.

*Opium.* Opium and the morphine group of alkaloids are not well tolerated by old people. As in infants and young children, morphine is liable to produce excessive depression of the respiratory centre. Morphine can, of course, be used as an analgesic in old people who require it; but special attention should be paid to

body weight, and in patients who are frail and debilitated a dose of the order of 5 mg. might be ample.

*Digitalis* may produce its characteristic signs of overdose at an early stage of treatment. Here again the ability adequately to dispose of the potent active principles (glycosides) is sometimes a significant factor. An additional point is that the scope for digitalis therapy diminishes *pari passu* with advancing degenerative disease of the myocardium, and there is a fairly high incidence of this kind of disability in the seventh and eighth decades of life.

*Purgatives.* In old people large doses of purgatives are to be avoided because excessive irritation of the bowel is apt to result in intractable diarrhœa, and this in turn may lead rapidly to constitutional disturbance from loss of body water and electrolytes. In old and rather frail people it is wise to try the effect of glycerin in the rectum (two glycerin suppositories) as a means of evacuating the lower bowel.

*External Applications.* In old people the skin is characteristically thin and atrophic, and the normal layer of subcutaneous fat is often lacking. In these circumstances the tissues are very liable to injury—both physical and chemical. Medicaments which are well tolerated by younger people may cause irritation and inflammation when applied to the delicate skin of an old person. If the tissues are atrophic on account of a poor peripheral blood supply, damage to the epithelium is likely to be much more severe than might be expected, and recovery from “chemical trauma” is correspondingly slow. It follows that in the use of drugs externally in old people a conservative approach should be adopted.

*Pharmaceutical Preparations.* Old people prefer to take their medicines in liquid form, pleasantly flavoured with aromatics; they often find difficulty in swallowing capsules and large pills. For infants and young children also, medicines must be prepared as fluids appropriately flavoured—often with raspberry, chocolate or oil of dill and sweetened with sugar or glycerin.

## CHAPTER 23

# THE INTRODUCTION OF A NEW DRUG

A DETAILED study of the evolution of drug therapy throughout man's sojourn on the Earth, would cover much of the history of medicine and merge into folk-lore. It would also inevitably raise a number of wider issues which have affected the course of civilisation and the behaviour of man: these include the value he places on health, the significance he attaches to disease, the impact of conscience on preventive medicine in its broadest aspects, his powers of reasoning displayed in the face of the unending challenge constituted by the existence of suffering, the burden of superstition, and so on.

It is instructive to observe also how developments in various branches of knowledge (and especially general science) have been applied to further man's skill in diagnostic and therapeutic procedures. No better example of this could be provided than that of the effect of the rapid expansion of chemistry in the past 100 years. The subject in its various divisions has become indispensable to the practice of medicine as we know it today. The research worker in therapeutics must accept the idiom of modern chemistry or he must be reconciled to working in isolation. Nevertheless, it is important to keep the whole subject of drug therapy in perspective. The present showing is that the various specialists within the field of chemistry will assume increasing responsibility for developing the science of pharmacology. No matter how far these developments proceed, the enlightened chemist will always be inclined to think in terms of natural products: these are often his prototypes, and they merit careful study on the lines of structure-function relationships (Appendix IV). For example the chemistry of the active principles contained in plants (including moulds and fungi) constitutes in itself more factual knowledge than any single worker can comprehend; and only a small proportion of the world's plants have been adequately

examined for naturally occurring substances with pharmacological actions. And looking beyond these first steps in exploration and discovery, there is the whole field of toxicology and of clinical trial in man. These aspects of pharmaceutical chemistry and experimental pharmacology need to be kept in mind when consideration is given to the development of new compounds by the synthetic chemist.

It must indeed be emphasised that every research project which aims at creating a new chemical substance for a specific therapeutic purpose must have a starting point in current concepts of structure-function relationships. The synthetic chemist does not work at random: he starts with what is called "a lead"--- "the discerning of a potentially useful biological effect in a chemical compound, either synthetic or natural in origin."\*

In the past many valuable drugs seem to have been discovered merely by chance. This conclusion is perhaps too readily accepted. If adequate records had always been kept they would doubtless reveal the debt which the modern scientist owes to his obscure predecessors for their powers of inductive reasoning. If they made discoveries by chance, it was true in their day as it is now that "chance comes to the mind prepared" and that "we see what we know".

The scientist who has made a special study of molecular constitution is often able to point out relationships between the structure of a molecule and its pharmacological action. Thus certain general principles have slowly emerged through the cooperation of the pure chemist and the experimental pharmacologist. It must be admitted, however, that within the framework of these principles there are many curious anomalies. Further, the active principles which account for the therapeutic effects of certain plants appear to be large molecules of great complexity. These substances require examination piece-meal in order to identify the radicals and groupings which are biologically active: this procedure calls for a high degree of professional skill and unlimited patience. A number of factual observations have been established between chemical structure and pharmacological

\* Goodwin, L. G., and Rose, F. I. *J. Pharm. Lond.*, 1958, 10, (suppt.), pp. 24-34.

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action. This information, though limited in extent, is of immense value. Nevertheless it is significant that notwithstanding the accumulation of a great mass of knowledge of chemistry, this cannot be safely used to forecast the exact effects of changing the molecular structure of a drug—especially when the compound has several pharmacologically active radicals. In this sphere the pure scientist is often obliged to proceed by a process of trial and error; and he has often to be content with useful knowledge that is largely empirical. The subject abounds with examples of trivial alterations of molecular structure resulting in major changes in pharmacological action. There are also many compounds which retain a specific and highly selective pharmacological activity notwithstanding extensive alterations in some parts of the molecule (p. 22).

It is emphasised elsewhere (p. 1) that when a drug acts on living cells, the effect is limited to either increasing or decreasing their normal physiological function; the drug never confers *new* functions on the cells. It follows that changes in the activity of a cell effected by a drug must result from interference with the normal processes of cellular metabolism. These processes are largely dependent on the integrity of enzyme systems; and it is highly probable that the effect of a drug on tissue cells is the indirect consequence of a temporary pharmacological interference with such enzyme systems. The investigation of pharmacological actions at cellular level therefore calls for a knowledge of biochemistry; and in research groups the collaboration of the pure chemist, the biochemist and the experimental pharmacologist is now regarded as indispensable.

When the chemists have designed and prepared a compound which has a molecular structure considered to be appropriate for a particular therapeutic purpose, it can be "screened" by pharmacologists. A series of standard tests are employed to determine its mode of action on isolated tissues obtained from various species of lower animals. Tests are also carried out on large numbers of small animals (usually beginning with mice) to estimate the toxicity of the compound—the LD 50 is the smallest dose of the drug which is lethal to 50 per cent of the test animals. Long-term toxicity tests are also planned; and in addition to systematic



observation on the living animals, post-mortem examinations are carried out on all the experimental animals and on the "controls" at the end of the test. Suitable toxicity tests are also performed on rabbits, cats, dogs and monkeys.

The synthetic chemist in his laboratory can usually supply about 5 G. of the new drug, and this suffices for the early stages of pharmacological screening on small animals. For the toxicity trials in the laboratories, however, 2-3 Kg. of the compound may be needed. When there is a prospect of extensive clinical trials, it is nearly always necessary to refer the problem to the "process chemists", who specialise in devising alternative methods of preparation appropriate to economical mass production. This phase may culminate in the installation of new manufacturing plant and finding staff to operate it.

For a hundred years or more, man has had a fairly clear insight into the significance of micro-organisms in relation to his own health and the health of his domestic animals. Experiments designed to develop our knowledge of bacteriostatic drugs began in earnest with the advent of the Listerian epoch. Subsequent events serve to illustrate some of the broader issues that emerge as these antimicrobial agents are tested in the laboratory and at the bedside. The therapeutic development of Tyndall's and Pasteur's concepts of antibiotic substances received great impetus with the discovery of sulphonamides (Gelmo; Domagk) and penicillin (Fleming; Florey; Chain) and kindred therapeutic agents (Waksman and others). The preliminary stage of screening these antimicrobial compounds is part of routine laboratory practice and biological assay. Such methods are invaluable and there are no signs that they will ever be abandoned by bacteriologists and parasitologists. This being so it is all the more important to appreciate the limitations of these *in vitro* methods. In general the results obtained by laboratory techniques are to be regarded not as conclusive, but as pointers indicating therapeutic possibilities or probabilities: they require to be interpreted with due caution and against a background of long and varied experience—gained in the laboratory and in clinical practice. One major consideration is that when a chemical compound is introduced into the living organism (an experimental animal or man) it is

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very likely to undergo degradation, to be transformed by the process of "protective synthesis", or to be disposed of by excretion or storage. These changes may result in its becoming therapeutically inert, or such may be the fate of the drug in the tissues that even in the process of "defending" itself against a substance foreign to its metabolism the therapeutic value of the drug may be greatly enhanced and the survival of the animal be assured. Thus there is often an element of urgency in pressing the need for testing new drugs on man himself, for one of the main lessons of experience in this field is that unexpected results are fairly common. A drug which seemed promising when tested on laboratory animals may have unlooked-for effects in human beings. Sometimes these effects are obviously of potential value, and may lead to new research programmes directed to detailed study of the new observation and its pharmacological and therapeutic implications.

The first phase of pharmacological experiment on human beings is to administer the new drug to the research workers themselves. Decisions on dosage and methods of administration are made in the light of all the data derived from tests on lower animals. Even so, only minute doses are given at first, and then the quantity is gradually increased until pharmacological actions are just perceptible. If no untoward effects are obtained in this way more extended tests are made. The subjects are usually medical or pharmaceutical students who volunteer to collaborate. One of the objects in enlarging the scope of the tests is to detect variations in the susceptibility of individuals to the action of the drug. The opportunity can be taken at this stage to use a *placebo*—an inert substance which, for this purpose, should be indistinguishable from the active drug. From the results of giving both these pharmaceutical preparations, valuable information may become available regarding doses tolerated by healthy adults and the validity of statements regarding alleged side-effects. The volunteers must of course be kept in ignorance of whether they are taking the drug or the placebo at any particular time. At this stage of the investigation, however, the supervisors must have this information so that they are in a position to take appropriate action according to circumstances, and ensure the maximum

degree of safety of those volunteers who do in fact take the drug.

The value of these tests on human beings is of course very great. It must be remembered, however, that those who receive the drug are healthy people. Much still needs to be done in testing the new compound on the type of patient for whom it was specially designed. Armed with information derived from tests on normal subjects the physician can reasonably offer the treatment to the appropriate patients. Here again, it is desirable to carry out a pilot trial on a small number of intelligent and cooperative patients to enable the physician to gain a general impression of the therapeutic value of the drug, and to enable him to adjust the dose to the needs of the sick man—as distinct from the normal man. If there is a *prima facie* case for proceeding further, plans are drawn up for a full scale *clinical trial*.

A “clinical trial” is now understood to imply a *controlled investigation*. The concept has been derived from workers in physics, chemistry and other scientific disciplines. In essence it consists in devising and conducting an experimental procedure, and then ensuring that the circumstances of the experiment are reproduced, but with the deliberate elimination of *one* of the factors concerned in the process. The procedures are called respectively the “*Experiment*” and the “*Blank*”; and they are often carried out simultaneously to ensure an approximation to identity of environment—using this word in its most comprehensive sense. In clinical trials the concept of an “Experiment” and a “Blank” is applied as far as may be possible within the limits imposed by ethics: thus an attempt is made to identify accurately the effects directly attributable to administration of the drug under investigation, and to make proper allowance for other factors which may be affecting the course of the patient’s illness. An individual patient may act as his own “Control”. That is to say, treatment may alternate between administration of the drug and administration of the placebo, allowance being made for any natural tendency to spontaneous improvement or deterioration. Again, groups of patients arranged according to age, sex, physique, severity of disease and many other circumstances may be allocated to groups *A* and *B* so that, judged by all the criteria known to be significant, the constitution of the groups is similar. Patients in

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Group *A* can be treated with the new drug under investigation while those in Group *B* receive the placebo. At an appropriate stage in the investigation the procedure can be reversed, so that patients in *B* receive the drug and those in *A* receive the placebo. Schemes of this kind are usually operated on the "Double Blind Technique". This means that neither the patients nor the doctors (who periodically assess alterations—if any) are aware of the nature of the pharmaceutical preparation which is being administered. Thus the switching over of Drug and Placebo between the two groups *A* and *B* mentioned above could be effected without disclosing the fact to the patients or physicians concerned. Further, an assessment of the therapeutic value of a new drug is often undertaken at several centres simultaneously. Each group of workers adheres to an agreed plan for the clinical trial. The results obtained by these independent groups can be reviewed periodically by an assessor who is concerned only with the data that are accumulating. It may or may not be justifiable to pool the results from the several groups of workers prior to making a statistical analysis of the findings and offering an opinion on their significance. The statistician can deal only with the arithmetical data presented to him. As a rule he is commenting on the results of a clinical trial in which he has not taken part. It is not his business to concern himself with *patients* but with *data*. The analysis is made on conventional lines familiar to mathematicians. The result is to be regarded simply as an arithmetical declaration of what is stated to have occurred in certain groups of people under clinical observation. Strictness of interpretation is imperative, otherwise serious errors are likely to occur: the results of statistical analysis do not in themselves provide any comment on the adequacy of the design of the experiment; and they do not test the soundness of the original decision to embark on the clinical trial.

There is an extensive literature on the planning of clinical trials. Every medical and pharmaceutical student should read Professor Bradford Hill's paper on "The Clinical Trial".\*

The techniques which are used in the clinical trial are devised on the assumption that the research worker is a practising clinician

\* A. Bradford Hill, *Brit. med. Bull.*

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with considerable knowledge of what Ryle called "The Natural History of Disease". The recording of symptoms and signs and their periodic re-assessment are matters for experienced clinicians who are genuinely interested in attempting to measure biological phenomena. The worker in this field must never cease to concern himself with the general principles of scientific enquiry—which are common to all research workers. In particular he must be well versed in the nature of evidence, possess good judgment on the design of experiments and acquire some familiarity with the principles of statistical analysis.

# APPENDIX I

## PHARMACEUTICAL TERMS A SELECTION OF PHARMACEUTICAL TERMS USED IN MEDICAL PRACTICE

### COMPOSITION OF DRUGS

THE composition of *inorganic drugs* is expressed by their names and formulæ (Appendix IV).

*Vegetable Drugs* are frequently of highly complex composition. The following are the chief active principles: fixed oils, volatile oils, resins, oleoresins, gums, gum-resins, balsams, alkaloids, glycosides, neutral principles, acids, starch, sugar, pectin, cellulose, albuminous substances, enzymes, colouring matters, salts and extractives.

A *Fixed Oil* is extracted by expression (if possible without the aid of heat) from the seeds or fruits of plants, or from animal tissues. Fixed oils are the esters of fatty acids (oleic, palmitic, stearic and others) with the radical glyceryl  $C_3H_5$ . They are split in the intestine by lipase. With caustic alkalis or metallic oxides they form *soaps*; the metal combines with the acids and displaces the glyceryl which is hydrated and becomes glycerin  $C_3H_5(OH)_3$ . Many of the fixed oils are also foodstuffs.

A *Volatile Oil* (essential oil, ethereal oil) is obtained mainly by distillation from entire plants, flowers, fruits or seeds. Most volatile oils are colourless when pure, and highly aromatic. They vary in composition. The majority contain liquid hydrocarbons called *elæoptenes*, which are pinenes or terpenes (for example, pinene in oil of turpentine). In addition, most contain oxidised aromatic hydrocarbons, termed *stearoptenes*, which chemically are alcohols, phenols, ketones, etc., and may be separated by cooling the oil or by fractional distillation. These are usually crystalline solids such as menthol, thymol and camphor; rarely they are liquid such as eucalyptol. Volatile oils are only sufficiently soluble in water to impart their odour and taste to it, but they are freely soluble in alcohol, ether and chloroform.

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*Resins* are solid and brittle substances, familiar as common resin (Colophony BP), which has various pharmaceutical uses by virtue of its physical properties. Resins which contain benzoic or cinnamic acids are called *balsams* (such as Balsam of Tolu).

A *Gum* is an exudation from the stems of plants. Gum Acacia and Tragacanth Gum are examples of such preparations. With water they form *mucilages* and are used pharmaceutically in preparing emulsions and suspensions.

*Alkaloids* are basic nitrogenous compounds, found in plants. Chemically the nucleus may be pyridine (Nicotine, Coniine), pyrrolidine (Atropine, Cocaine), quinoline (Quinine), isoquinoline (Papaverine, Narcotine), or phenanthrene (Morphine, Codeine). Like alkalis, alkaloids turn red litmus blue; they also form salts with acids. As a rule they are crystalline solids; rarely they are liquids (such as Pilocarpine and Nicotine). Alkaloids are only sparingly soluble in water, but are readily soluble in alcohol; their salts dissolve easily in water.

*Glycosides*, such as digitoxin, ouabain and amygdalin are ester-like combinations of sugars; on hydrolysis they yield sugars and other compounds—*genins*—which may be phenols, alcohols, aldehydes, etc. Amygdalin yields hydrocyanic acid, benzaldehyde and dextrose.

*Saponins* are nitrogen-free glycosides. Solutions of saponins, by lowering surface tension, froth on shaking and emulsify fats and resins. They cause hæmolysis of red blood cells.

*Neutral Principles* are active substances which do not conform to any special group.

*Organic Acids* such as malic, oxalic, citric, exist in plants combined with base such as potassium, calcium and alkaloids; or organic acids may be free, for example, tannic acid.

*Proteins.* Most drugs contain unimportant albuminous constituents; but the seeds of ricinus, croton and abrus yield highly poisonous *toxalbumoses*, ricin, crotin and abrin respectively, which are allied to the toxalbumoses of snake-venom and toxins of bacteria. These toxalbumoses are extremely poisonous when injected parenterally, but if the doses are suitably graded and given at intervals, the body can develop a state of immunity to them.

## PREPARATIONS OF DRUGS

The physical characters of most drugs are such that it is necessary to prepare these substances for therapeutic use. The procedure is analagous to that adopted in preparing foodstuffs from natural sources such as wheat and nuts. Thus if we take, as examples, *sulphur* (one of the elements); *colocynth* (the dried pulp of a fruit); *cascara* (a dry bark); and *coccus* (a dried insect), it is clear that these drugs, as they are available in commerce, cannot be administered to a patient until they have been presented as pharmaceutical preparations which meet therapeutic requirements. There are additional reasons for having a variety of preparations: (1) drugs exist in various forms; (2) the material (leaves, roots, etc.) may contain several active principles, soluble in different media, and it may or may not be desirable to extract these principles together or separately; (3) it is sometimes desirable to obtain combinations of drugs, so as to increase, diminish, or otherwise modify the action of each, or to obtain combined actions; (4) as indicated above, provision must be made for the individual patient's needs, and the physician chooses from a variety of preparations for internal or external use—such as *tablets*, *tinctures*, *infusions*, *ointments*, etc.

Much of the history of pharmacy is concerned with the evolution of various preparations of drugs devised to meet requirements defined by the physician. There is an extensive literature on the subject, extending from the occult art of the individual pharmacist (as portrayed in mediæval times and more remote epochs) to the organisation of the pharmaceutical industry as it is seen today. It is highly desirable that the clinical student should appreciate the scope of pharmaceutical science—if only to make him aware of his dependence on the skill and ingenuity of those who prepare drugs for medical and veterinary practitioners.

A glance at the literature suffices to show that many pharmaceutical preparations formerly in demand by doctors have become obsolete. There is now a tendency to prescribe only the drug which is indicated by the clinical condition and to devise the simplest possible method of administration, for example as a tablet or in a gelatin capsule. The professional resources of the



pharmacist are often taxed to the limit in the effort to achieve this simplicity of formulation. The preparations thus devised are "elegant" in the sense that they are the product of exceptional pharmaceutical skill. The term "elegant" is, however, also used in an unfortunate sense: it is applied to preparations of drugs made up with excessive amounts of flavourings and colouring agents so that they resemble products of the confectionery trade. Such practices are scarcely in keeping with ethical standards defined by teachers of pharmacy.

The following are the different kinds of pharmaceutical preparations included in the *British Pharmacopæia*,

### 1. *Preparations Given by Mouth*

**Elixir.** An elixir is a fluid preparation which has been made specially palatable by the addition of sweetening agents and aromatic substances.

**Emulsion.** An emulsion is a colloidal dispersion of two immiscible fluid drugs. Two "phases" are described—an internal finely subdivided *disperse phase* in an external (usually aqueous) *continuous phase*. The stability is maintained by an emulsifying agent such as acacia or tragacanth.

**Extract.** The Extracts are an important group of products. Compared with the plant or other material from which it is made, an extract is of small bulk and contains the active principles in high concentration. These results are achieved by using solvents—water or alcohol—and at a suitable stage disposing of the excess of solvent. There are solid extracts and liquid extracts. Many of them are assayed: the preparation can then be adjusted to contain a required concentration of active principles. Liquid extracts are usually administered in fluid mixtures; solid extracts are given as tablets or pills.

**Infusion.** A *Fresh Infusion* is prepared by steeping the drug in cold water for 15–30 minutes and straining. A *Concentrated Infusion* is made by macerating (soaking) the drug with cold water or with water and alcohol. There are only two official infusions—

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the Compound Gentian Infusion and a Concentrated Compound Gentian Infusion.

*Liquor.* A Liquor is a solution: it consists of a substance (other than a volatile oil) dissolved in water or in alcohol, solution being assisted by various means.

*Mixture.* A Mixture is either a solution of various drugs or a dispersion of insoluble powders in water.

*Mucilage.* A Mucilage is a solution of a gum.

*Powder.* A Powder consists of dry insoluble drugs reduced to powder and intimately mixed and sifted.

*Spirit.* There are two preparations of this type in the BP—Chloroform Spirit and Peppermint Spirit. They are typical of a larger (but non-official) group made by dissolving a volatile substance in 90 per cent alcohol. The strength of the official Spirits is 10 per cent v/v.

*Syrup.* A Syrup is a fluid preparation containing much sugar.

*Tablet.* Tablets are solid discs made by compressing in granular form, or moulding, a drug or mixture of drugs commonly with the addition of an inert diluent and possibly with a disintegrating agent (such as starch).

*Tincture.* A Tincture is a solution of active substances in alcohol, either alone or combined with other solvents. The pharmaceutical processes employed in the preparation of tinctures (simple solution, maceration, percolation, standardisation, etc.) are described in appropriate books of reference.

*Water (Aromatic).* An Aromatic Water is a very weak simple solution of a volatile substance in distilled water, obtained by various pharmaceutical methods. A *Concentrated Water* is a strong solution of a volatile substance in alcohol and water; it is

about forty times stronger than the corresponding Aromatic Water.

Examples of Aromatic Waters are Chloroform Water and Camphor Water; and there are Concentrated Waters of Peppermint, Cinnamon and Dill.

## 2. *Preparations Given per Rectum*

*Suppository.* A Suppository is a conical body for introduction into the rectum, where the preparation melts. It is made either of cocoa butter or of gelatin; and the active drug is incorporated into this "base" during manufacture.

## 3. *Preparations given by Parenteral Injection*

*Injection.* An Injection is a sterile preparation intended to be given subcutaneously, intramuscularly or intravenously. The general principles governing this kind of therapy are mentioned on p. 12, and examples are given in Appendix II.

## 4. *Preparations used Externally*

*Collodion.* A Collodion is a solution of pyroxylin and resin in alcohol and ether, intended—on evaporation of the solvents-- to leave a coating of pyroxylin on the skin.

*Cream.* A Cream—for external application---is prepared with a basis of emulsifying wax, hard paraffin, liquid paraffin and water.

*Eye Ointment.* An Eye Ointment has a sterilised basis of liquid paraffin, yellow soft paraffin and wool fat. Into this basis drugs can be incorporated for various purposes—mydriatics and bacteriostatics.

*Gelatin.* A Gelatin is a suspension of zinc oxide in gelatin, glycerin and water.

*Liniment.* A Liniment or Embrocation is a preparation suitable for application by rubbing, anointing or painting.

*Lotion.* A Lotion is a liquid preparation "intended for application to the skin or for irrigation of the ear, nose and throat or the

urethra. They may be aqueous or alcoholic solutions, or suspensions in aqueous vehicles" (BPC). Lotions are applied on lint or dabbed on the skin with a shaving brush; they are not rubbed into the skin (cf. Liniments).

*Ointment.* An Ointment is a mixture of active substances with various ointment bases such as lard, wool fat, soft paraffin, etc. The ingredients are either thoroughly mixed with a spatula or melted together.

*Paste.* A Paste is an unctuous preparation containing a high proportion of starch, for external use.

*Poultice* (Cataplasma). A Poultice is a paste made of kaolin and glycerin with a number of volatile substances added for their counter-irritant action. The glycerin gives the poultice the correct consistence and prevents it from becoming hard.

5. *The following preparations are also in common use but are not included in the current edition of the BP*

An *Application* is an aqueous suspension of a skin remedy (Application of Benzyl Benzoate). A *Bougie* is a solid cylinder of gelatin or cocoa butter with which a drug is incorporated for introduction into the urethra or the nose. A *Cachet* is a lenticular capsule of rice paper to enclose a nauseous or insoluble drug. A *Capsule* is a receptacle commonly made of gelatin to enclose a nauseous or insoluble drug, either solid or liquid. A *Disc* or *Lamella* is a very small disc of soft gelatin (a wafer a few millimetres in diameter) containing a minute dose of an alkaloidal salt. This preparation is placed in the conjunctival sac where the gelatin melts and releases the drug (mydriatics, miotics and local anæsthetics). A *Draught* (haustus) is a quantity of a drug dispensed in a few ounces of water to be taken as a single dose. An *Enema* is a liquid preparation for administration per rectum. A *Gargle* is a solution of a drug intended to produce a local effect on the fauces in the act of gargling. It is rarely successful; gargles produce only the benefits of a mouth-wash. *Glycerin.* A solution of a drug in glycerin is called a *Glycerin*. The drug is dissolved without the aid

of heat or water. An *Inhalation* (vapour) is administered as a vapour either *dry* (drugs volatile at room temperature) or *moist* (drugs volatilised from hot water at about 160° F.). An *Insufflation* is a powder to be blown into the throat, ear or nose. A *Linctus* is a thin confection; its consistency is such as to produce a soothing effect in the fauces—in addition to the systemic action of the drug contained in the linctus when this has been absorbed from the alimentary tract. A *Lozenge* (trochiscus) is a dry tablet of one or more active ingredients mixed with a basis prepared with sucrose, gum acacia and various flavouring agents. An *Oxymel* is a preparation containing purified honey and acetic acid and water; other medicaments may be added. A *Paper* is cartridge paper coated with mustard in rubber solution and used like a plaster. A *Paint* (pigmentum) is a solution to be painted on a part. A *Pastille* is a soft lozenge containing glycerin and gelatin, and an antiseptic may be added to this basis. A *Pessary* is a large form of the suppository administered per vaginam. A *Pill* is made of a suitable excipient (hard soap, extract of gentian, etc.) into which drugs in suitable form can be incorporated; procedures and standards are described in the BPC. *Solution Tablets* provide a convenient method of making up standard solutions for therapeutic use. Solutions of drugs in water are used as a *Mouth-wash* (collutorium), a *Nasal-wash* (collunarium) or as an *Eye-wash* (collyrium). A *Spray* (nebula) is used for giving drugs in solution from an atomiser. *Vitellæ* are small crushable glass capsules covered with cotton and silk to protect the fingers when the containers are broken: amyl nitrite is conveniently given by inhalation from vitellæ.

## APPENDIX II

### FORMULARY

#### Introduction

THE Formulary consists of pharmaceutical preparations selected to meet the ordinary requirements of the medical practitioner. Most of the information is condensed from standard books of reference; and emphasis is placed on information which has some bearing on *prescribing* or which indicates the reason why a particular pharmaceutical preparation is in common use. In this book no attempt is made to offer comprehensive lists of drugs and their preparations: these are readily available in standard books of reference (BP, BPC, *The Extra Pharmacopœia*, etc.). Some general remarks on this subject are included in Chapter 1. It is only necessary to emphasise the need to acquire the correct approach to prescribing. Once the physician has decided on the patient's needs in terms of the desired pharmacological action, he should proceed to the selection of a pharmaceutical preparation. At this stage he should deliberately consult a Formulary of his own choice—such as the BNF, the BPC or *The Extra Pharmacopœia*. He naturally gives preference to the preparation which is effective when administered by mouth. If, however, there are circumstances which make it desirable to adopt some other method of administration, the doctor must be competent to prescribe the appropriate alternative preparation of the drug (parenteral injection, inhalation, etc.) and he must know how to give it.

All standard remedies—such as those listed in the BP and the BPC—are supplied in bulk to private pharmacists and to hospitals by the principal manufacturers: these are readily available against a prescription written by a registered medical practitioner. Many thousands of pharmaceutical preparations are also produced under trade-names. As these protected trade-names do not necessarily indicate the relationship of the active ingredients to standard pharmaceutical preparations, it is necessary to obtain details about such “proprietarys”. They can then be allocated to their proper

category from the prescriber's point of view. It is obvious that the medical practitioner is under an obligation to obtain accurate information regarding the nature of pharmaceutical preparations which he prescribes for patients under his care. The information is almost invariably available in the manufacturer's literature, in *The Extra Pharmacopæia* or in *New and Non-official Remedies* (American Medical Association).

The names of a small number of proprietary preparations are included in the Formulary. Details regarding the composition of proprietaries are usually available in the reference books listed in Appendix V. While using the Formulary the student should keep in mind the general information on Prescribing included in Chapter 22, and especially the principles underlying the categorisation of proprietary preparations—also dealt with in Chapter 22.

The student is advised to read the General Notices in the *British Pharmacopæia* 1958. The guidance offered on *Doses* is particularly important (General Notices pp. 7 and 8). As in the BP, doses mentioned in the Formulary are the quantities "generally regarded as suitable for adults when administered by mouth". It should not be assumed that a drug can be given by any other route of administration unless this is specifically stated. Most drugs that are prescribed for oral administration are taken after food three or four times in 24 hours.

Preparations of official and non-official drugs are often made available in different strengths. The range in each case can be ascertained by referring to the manufacturers' literature. In the Formulary the preparation mentioned is that which is commonly used when prescribing for adult patients.

## PHARMACOLOGY OF RENAL FUNCTION

(see Chapter 2)

### DIURETICS

#### Mersalyl Acid

A white odourless powder. Slightly hygroscopic, sparingly soluble in water, readily soluble in sodium hydroxide solution. Contains not less than 41.5 and not more than 44 per cent of mercury.

#### Mersalyl Injection

A clear colourless liquid containing about 10 per cent Mersalyl Acid and 5 per cent Theophylline in sodium hydroxide solution. Protect from light. 2 ml. contain 0.2 G. of mersalyl (sodium salt of mersalyl acid) and 0.1 G. of theophylline.

*Dose.* By intramuscular injection, 0.5-2 ml.

#### Acetazolamide

2-Acetamido-1:3:4-thiadiazole-5-sulphonamide.  
Crystalline powder almost insoluble in water.

*Dose.* 0.25-1 G. daily.

#### ACETAZOLAMIDE TABLETS

1 Tablet contains 0.25 G.

#### Theophylline

1:3-Dimethylxanthine.

An alkaloid obtained from tea or coffee or prepared synthetically. White powder, soluble in hot water.

*Dose.* 60-200 mg.

#### Aminophylline

(Theophylline with Ethylenediamine.)

It contains about 80 per cent of Theophylline and about 13 per cent of Ethylenediamine.

White granules soluble in water.

*Dose.* 0.1-0.3 G.

By slow intravenous injection, 0.25-0.5 G.



## DILLING'S CLINICAL PHARMACOLOGY

### AMINOPHYLLINE INJECTION

Solution of Aminophylline in Water for Injection free from carbon dioxide. The injection is given intravenously *slowly* (1-2 minutes).

Usual strength is 0.25 G. in 10 ml. for intravenous use.

For intramuscular injection a solution is available containing 0.5 G. in 2 ml. (a less satisfactory preparation and *painful* at injection site).

### AMINOPHYLLINE TABLETS

1 Tablet contains 0.1 G.

*Dose.* 0.1-0.3 G.

### AMINOPHYLLINE SUPPOSITORIES (USP)

Usual strength: 0.5 G.

## Chlorothiazide

6-Chloro-7-sulphamyl-1:2:4-benzothiadiazine-1:1-dioxide.

It is a substituted sulphonamide (see text).

*Dose.* Usually 1-2 G. daily.

### CHLOROTHIAZIDE TABLETS

1 Tablet contains 0.5 G.

## Aminometradine

1 Tablet contains 0.2 G.

*Dose.* Usually 0.4-0.8 G. daily.

## Amisometradine

1 Tablet contains 0.4 G.

*Dose.* Usually 0.4 G. thrice daily.

## Potassium Citrate

White crystalline substance with saline taste. Slightly hygroscopic.

*Dose.* 1-2 G.

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### **Urea**

(Carbamide.)

The diamide of carbamic acid. Colourless; saline taste. Soluble water.

*Dose.* 5-15 G.

### **Ammonium Chloride**

$\text{NH}_4\text{Cl}$ .

White powder soluble in water, saline taste.

*Dose.* Before the administration of Mersalyl Injection, 3-6 G. daily, in divided doses.

It may be given in a mixture or as

TABLETS OF AMMONIUM CHLORIDE—

The Tablets may be enteric-coated.

1 Tablet contains 0.5 G.

### **Cation Exchange Resins**

Synthetic organic polymers consisting of hydrocarbon network to which ionisable acidic groups are attached. Chemically—polystyrene sulphonate or carboxylate.

To assist in sodium-reduction therapy, several proprietary preparations are available:

“Amberlite”, “Carbo-Resin”, “Kationium”.

*Dose.* Usually up to 45 G. orally daily.

## URINARY ANTISEPTICS

### **Mandelic Acid**

$\alpha$ -Hydroxyphenylacetic acid.

White crystals, soluble in water. Protect from light.

*Dose.* 2-4 G.

### **Ammonium Mandelate**

A white, hygroscopic, crystalline powder, soluble in water. Protect from light and moisture.

*Dose.* 2-4 G.

### **Hexamine Mandelate**

("Mandelaminic.")

Hexamethylenetetramine mandelate.

A white crystalline powder, containing not less than 46 per cent hexamine, and not less than 50 per cent mandelic acid.

*Dose.* Usually 1 G., up to 4 times daily.

"Mandelaminic"—enteric-coated capsules —each 250 mg.

### **Hexamine**

Hexamethylenetetramine.

Colourless crystals, soluble in water, decomposed by acids.

*Dose.* 0.6 2 G.

#### HEXAMINE TABLETS

A Tablet contains 300 mg.

### **Nitrofurantoin**

(NNR.)

1-(5-Nitrofurfurylidencamino)hydantoin.

A yellow powder, practically insoluble in water.

*Dose.* 5-8 mg./Kg. body weight daily.

#### NITROFURANTOIN TABLETS

A Tablet contains 50 mg. unless otherwise specified.

## **HÆMATINICS, HUMAN BLOOD AND PLASMA**

(see Chapter 3)

### **Ferrous Sulphate**

$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ .

Green crystals, soluble in water, astringent taste. Aqueous solutions deteriorate, forming ferric salt.

*Dose.* 0.2-0.3 G.

#### FERROUS SULPHATE TABLETS

A Tablet contains 200 mg.

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### **Ferrous Gluconate**

Greyish-green powder slowly soluble in water.

*Dose.* 0.3–0.6 G.

#### FERROUS GLUCONATE TABLETS

A Tablet contains 0.3 G.

### **Ferric Ammonium Citrate**

Dark red transparent scales, soluble in water, astringent taste.

*Dose.* 1 G. (in solution) four times daily after meals.

### **“Imferon”**

(Proprietary preparation.)

An iron-dextran complex suitable for intramuscular injection.

1 ml. contains 50 mg. available iron.

### **Saccharated Iron Oxide**

Free from elemental iron, it may be given intravenously as a 2 per cent solution; 5 ml. contains 100 mg.

### **Cyanocobalamin**

(Vitamin B<sub>12</sub>.)

Red crystals, soluble in water.

*Dose.* 50–100 µg. weekly or more frequently as a minimum.

#### CYANOCOBALAMIN INJECTION

A sterile solution of Cyanocobalamin in water: 1 ml. contains 50 µg; stronger preparations are available

### **Folic Acid**

(Pteroylglutamic Acid.)

An orange-yellow crystalline powder, soluble in water.

*Dose.* 5–20 mg. daily.

#### FOLIC ACID TABLETS

A Tablet contains 5 mg.

## Human Blood and its Preparations

**WHOLE HUMAN BLOOD** taken aseptically into a fluid anti-coagulant usually containing dextrose which improves cell survival. It must be cooled to  $4^{\circ}$ – $9^{\circ}$  C. and kept at that temperature until immediately before infusion. Whole human blood must be used within twenty-one days of its collection.

**CONCENTRATED HUMAN RED BLOOD CORPUSCLES** are prepared from whole human blood not more than fourteen days after collection by removing supernatant plasma and anticoagulant. They must be used within twelve hours of preparation.

**DRIED HUMAN PLASMA** is prepared by freeze-drying pooled liquid plasma, mixed in such proportions as to neutralise blood-group agglutinins. It must be sterile, and it is kept in a sterile container sealed to exclude micro-organisms and moisture. Storage temperature should not exceed  $20^{\circ}$  C., and light should be excluded. The dried plasma is readily soluble in water to make a solution of a volume equal to that from which it was originally prepared. It contains not less than 4.5 per cent protein. In the dry state the preparation keeps for two years, but it must be used immediately after reconstitution.

**HUMAN FIBRINOGEN** is a dried preparation from human plasma of fibrinogens precipitated by organic solvents at controlled conditions of temperature, pH and ion concentration. The precipitate is dissolved and freeze dried. It should be stored under sterile conditions similar to those for dried human plasma. It is reconstituted with saline solution and should be used immediately thereafter.

**HUMAN THROMBIN** is a cream-coloured powder readily soluble in saline solution. It is obtained from human plasma by precipitation of prothrombin which is converted to thrombin by the addition of calcium ions and thromboplastin. The solution is clarified by filtration and dried from the frozen state. Storage conditions are the same as those of dried human plasma. Thrombin should be used immediately after reconstitution.

**HUMAN FIBRIN FOAM** is prepared as a firm, fine, white dry sponge; fibrinogen solutions are foamed and are then clotted with human thrombin. It is stored under sterile conditions the same as those for dried human plasma.

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**HUMAN GAMMA GLOBULIN** is prepared from pooled liquid plasma by precipitation. The precipitate is dissolved in saline solution and dried from the frozen state. It is a white or slightly yellow powder containing 95 per cent protein of which 90 per cent is gamma globulin, and it is freely soluble in water. It is stored in sealed sterile containers under the same conditions as for dried human plasma. Human gamma globulin should be used immediately after reconstitution.

**DEXTRAN INJECTION** is a sterile solution in Sodium Chloride Injection of degraded dextrans of a standardised molecular size. The solution is colourless and slightly viscous. It should be stored at a temperature below 20° C. and may be kept for up to five years.

## ANTICOAGULANT DRUGS

(See Chapter 4)

### **Heparin**

Obtained from lung or liver tissue by enzymatic digestion. A complex organic salt, containing not less than 100 U. per mg. A greyish-brown hygroscopic powder, soluble in water.

*Dose.* 5,000–15,000 U. intravenously or intramuscularly.

#### **INJECTION OF HEPARIN.**

A sterile solution in Water for Injection. Strength must be stated, e.g. 10,000 U. per ml.

### **Dextran Sulphate**

The sodium salt of sulphuric acid esters of dextran. Not less than 10 U. per mg.

*Dose.* 5,000–15,000 U. intravenously.

### **Phenindione**

2-Phenylindane-1:3-dione.

Soft white crystals, slightly soluble in water.

*Dose.* Initial 200–300 mg.

Maintenance 25–100 mg. daily, according to prothrombin activity of blood.

### **Ethylbiscoumacetate**

A white crystalline powder, almost insoluble in water.

*Dose.* 0.15–1 G. daily, according to prothrombin activity of the blood.

### **Protamine Sulphate**

The sulphate of protamine, a simple protein obtained from fish testes. Soluble in water.

*Dose.* Up to 50 mg. intravenously.

INJECTION OF PROTAMINE SULPHATE (BPC Supplement)  
contains 50 mg. in 5 ml.

### **Phytonadione USP**

(Vitamin K<sub>1</sub>)

2-Methyl-3-phytyl-1:4-naphthaquinone (see Vitamin K, p. 675).  
A clear, yellow, viscid liquid, insoluble in water; protect from light.

*Dose.* 2 mg. intravenously or subcutaneously.

Up to 100 mg. may be used for correction of prothrombin activity following anticoagulant administration.

## **VITAMINS**

(See Chapter 5)

### **VITAMIN A**

#### **Halibut Liver Oil**

A yellow, oily liquid expressed from the liver of *Hippoglossus hippoglossus*: 1 G. contains not less than 30,000 U. Vitamin A activity.

*Dose.* 0.06–0.5 ml. (1,500–12,000 U.) daily.

#### **Cod Liver Oil**

A yellow oil extracted from the liver of *Gadus morrhua* L. 1 G. contains not less than 600 U. Vitamin A, and not less than 85 U. Vitamin D.

*Dose.* 4–16 ml. daily, in divided doses.

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### VITAMIN D

#### **Calciferol**

(Vitamin D<sub>2</sub>).

Prepared by the irradiation of ergosterol. White, needle-like crystals, insoluble in water but soluble in alcohol: 1 mg. contains 40,000 U. antirachitic activity.

*Dose.* Prophylactic 0.025–0.1 mg. (1,000–4,000 U.) daily.

Therapeutic 0.125–1.25 mg. (5,000–50,000 U.) daily.

#### SOLUTION OF CALCIFEROL

1 G. contains 3,000 U. antirachitic activity.

*Dose.* Prophylactic 0.3–1.2 ml. daily.

Therapeutic 1.5–15 ml. daily.

#### CONCENTRATED SOLUTION OF VITAMIN D

1 G. contains 10,000 U. antirachitic activity, and not more than 5,000 U. of Vitamin A.

*Dose.* Prophylactic 0.1–0.4 ml. daily

Therapeutic 0.5–5 ml. daily.

### VITAMIN B COMPLEX

#### **Aneurine Hydrochloride**

(Vitamin B<sub>1</sub>, Thiamine Hydrochloride.)

A complex pyrimidine-thiazole compound. Colourless, plate-like crystals, soluble in water.

*Dose.* Prophylactic 2–5 mg. daily.

Therapeutic 20–100 mg. daily.

#### ANEURINE HYDROCHLORIDE INJECTION

A sterile, aqueous solution. 1 ml. contains 25 mg.

By subcutaneous or intramuscular injection.

#### ANEURINE HYDROCHLORIDE TABLETS

A Tablet contains 3 mg.



### Nicotinic Acid

(Niacin, P.P. factor.)

Pyridine-3-carboxylic acid, obtained from the oxidation of  $\beta$ -picoline. White or cream crystals, soluble 1 in 75 of water.

*Dose.* Prophylactic 15-30 mg. daily.

Therapeutic 50-250 mg. daily.

#### NICOTINIC ACID TABLETS

A Tablet contains 50 mg.

### Nicotinamide

Pyridine-3-carboxylic acid amide. White crystalline powder, soluble in water.

*Dose.* Prophylactic 15-30 mg. daily.

Therapeutic 50-250 mg. daily.

#### NICOTINAMIDE TABLETS

A Tablet contains 50 mg.

### Riboflavine

(Lactoflavin, Vitamin B<sub>2</sub>.)

6:7-Dimethyl-9-(D-l-ribityl)isoalloxazine. An orange-yellow, crystalline powder, slightly soluble in water. Solutions must be protected from light.

*Dose.* Prophylactic 1-4 mg. daily.

Therapeutic 5-10 mg. daily.

## VITAMIN C

### Ascorbic Acid

The enolic form of 3-keto-L-gulofuranolactone. Minute, colourless crystals, readily soluble in water. Unstable to heat. Solutions, unless acid, oxidise readily.

*Dose.* Prophylactic 25-75 mg. daily.

Therapeutic 200-500 mg. daily.

#### ASCORBIC ACID TABLETS

A Tablet contains 25 mg.

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### VITAMIN K

#### **Menaphthone**

2-Methyl-1:4-naphthaquinone. A yellow, crystalline powder. Decomposes in sunlight, irritant to skin and mucosæ. Insoluble in water, but soluble in oil.

*Dose.* By intramuscular injection, 5-10 mg. daily.

#### INJECTION OF MENAPHTHONE

A sterile solution in Ethyl Oleate. 1 ml. contains 5 mg.

#### **Acetomenaphthone**

1:4-Diacetoxy-2-methylnaphthalene. A white, crystalline powder, almost insoluble in water.

*Dose.* Determined by the physician in accordance with the needs of the patient.

#### ACETOMENAPHTHONE TABLETS

A Tablet contains 5 mg.

## DRUGS ACTING ON THE AUTONOMIC NERVOUS SYSTEM

(see Chapter 6)

### PARASYMPATHOMIMETIC DRUGS

#### **Acetylcholine**

(not official)  $\text{HO}(\text{CH}_2)_3\text{N}.\text{CH}_2\text{CH}_2\text{O}.\text{CO}.\text{CH}_3$ .

The acetyl ester of Choline.

#### **Carbachol**

Carbamylcholine Chloride.

2-Carbamoyloxyethyltrimethylammonium chloride.

*Dose.* Orally 1-4 mg.; subcutaneously 0.25-0.5 mg.

The Injection contains 0.25 mg. in 1 ml.

*N.B.* Not to be given intravenously.

### **Bethanechol Chloride**

2-Carbamoyloxypropyltrimethylammonium chloride.

A white crystalline powder soluble in water.

*Dose.* 5-30 mg. by mouth.

The Tablet contains 5 mg.

2.5-5 mg. subcutaneously.

The Solution contains 5 mg. in 1 ml.

### **Methacholine Chloride**

2-Acetoxypropyltrimethylammonium Chloride. "Mecholin", "Mecholyl".

*Dose.* Orally 100-200 mg.; subcutaneously 10-25 mg. Is regarded as more satisfactory than Carbachol as a vagal stimulant in paroxysmal tachycardia; an injection frequently restores a normal rhythm within a few minutes.

### **Muscarine**

Alkaloid derived from the poisonous fungus *Amanita muscaria* (the "fly fungus").

No therapeutic uses (see text).

### **Physostigmine Salicylate**

Eserine salicylate.

The salicylate of an alkaloid, Physostigmine, obtained from Calabar Bean, the seed of *Physostigma venenosum*.

### **Neostigmine Bromide**

("Prostigmin.")

The dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium bromide.

*Dose.* Orally 15-30 mg.

### **Neostigmine Methylsulphate**

A white, crystalline, soluble powder.

*Dose.* By subcutaneous or intramuscular injection: 0.5-2 mg.

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### Pilocarpine Nitrate

The nitrate of an alkaloid, Pilocarpine, obtained from the leaves of *Pilocarpus microphyllus* (Jaborandi), and other species.

A white crystalline soluble powder.

*Dose.* 3–12 mg.

### Edrophonium

("Tensilon.")

Edrophonium Chloride. Ethyl-(3-hydroxyphenyl)dimethylammonium chloride.

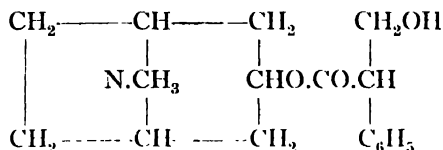
A white, crystalline powder readily soluble in water and alcohol.

*Dose.* 5–10 mg. intravenously.

## ATROPINE GROUP

### Atropine

An alkaloid, (±)-hyoscyamine, from *Atropa belladonna*, *Hyoscyamus muticus* or other solanaceous plants.



Colourless acicular crystals. Physical characteristics those of alkaloids.

Chemically it can be resolved into *tropine*  $\text{C}_8\text{H}_{15}\text{NO}$  and *tropic acid*  $\text{C}_9\text{H}_9\text{O}_3$

### Atropine Sulphate

Colourless crystals, somewhat hygroscopic. Freely soluble in water.

*Dose.* 0.25–1 mg.

Used mainly for parenteral injection.

Also for preparations which are applied locally—eye-drops and eye-ointments (mydriatic). Topical use of Belladonna derivatives on *skin* is obsolete.

### **Atropine Methonitrate**

("Eumydrin.")

An alternative to Atropine in the drug treatment of hypertrophic pyloric stenosis of infancy: solution 1 in 10,000 used; 2 ml. before feeds, increasing to 5 ml.

### **Belladonna Herb**

Belladonna Leaf.

The dried leaf and other aerial parts of *Atropa belladonna* or *Atropa acuminata*. Contains not less than 0.3 per cent of alkaloids (hyoscyamine, atropine, hyoscine and belladonnine).

### **Belladonna Dry Extract**

Contains 1 per cent alkaloids. Used in powders and in pills.

*Dose.* 15-60 mg. (60 mg. contains 0.6 mg. alkaloids).

### **Belladonna Tincture**

*Dose.* 0.6-2 ml. (2 ml. contains 0.6 mg. alkaloids).

### **Homatropine Hydrobromide**

The hydrobromide of an alkaloid prepared from tropine and mandelic acid.

A short-acting mydriatic; rarely if ever used otherwise.

### **Hyoscyamus**

Hyoscyamus Leaves. Henbane Leaves. The dried leaves and flowering tops of *Hyoscyamus niger*.

The active alkaloids are (1) 1-hyoscyamine, (2) hyoscine or scopolamine and (3) atropine. Contains not less than 0.05 per cent of alkaloids as hyoscyamine.

#### **HYOSCYAMUS DRY EXTRACT**

Standardised to contain 0.3 per cent of alkaloids. 60 mg. contains 0.18 mg. alkaloids.

*Dose.* 15-60 mg.

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### HYOSCYAMUS TINCTURE

Contains 0.005 per cent of alkaloids. 4 ml. contains 0.2 mg. alkaloids.

*Dose.* 2-4 ml.

### Hyoscine Hydrobromide

Scopolamine Hydrobromide.

Obtained from *Hyoscyamus* Leaves, and other solanaceous plants. Colourless, rhombic crystals. Fairly soluble in water.

*Dose.* 0.3-0.6 mg.

### HYOSCINE EYE OINTMENT

Contains 0.25 per cent in Yellow Soft Paraffin and Wool Fat.

### Stramonium

Stramonium Leaves. The dried leaves and flowering tops of *Datura stramonium* or *D. tatula*. Alkaloids are chiefly hyoscyamine along with atropine and hyoscine (scopolamine). Contains not less than 0.25 per cent of alkaloids calculated as hyoscyamine.

### STRAMONIUM DRY EXTRACT

1 per cent alkaloids. 60 mg. contains 0.6 mg. alkaloids.

*Doses.* 15-60 mg.; in post-encephalitic and similar conditions: 60-500 mg.

### STRAMONIUM TINCTURE

Contains 0.025 per cent alkaloids. 2 ml. contain 0.5 mg. alkaloids.

*Dose.* 0.6-2 ml.

### Amprotropine Phosphate

("Syntropan.")

3-Diethylamino-2:2-dimethylpropyl ( $\pm$ )-tropate dihydrogen phosphate.

A weak spasmolytic with the effects of atropine and papaverine. A white crystalline powder.

*Dose.* 50-100 mg.

A Tablet contains 50 mg.

### **Adiphenine Hydrochloride**

("Trasentin.")

2-Diethylaminoethyl diphenylacetate hydrochloride pentahydrate.  
A weak spasmolytic used in gastro-intestinal disorders.

*Dose.* 75-150 mg.

A Tablet contains 75 mg.

### **Dibutoline Sulphate**

(2-Dibutylcarbamoyloxyethyl)ethyl dimethylammonium sulphate.  
Highly hygroscopic. Solution 5 per cent used in ophthalmology.

*Dose.* 5-30 mg., or instilled into the eye in 5 per cent solution.

### **Diphepanil Methylsulphate**

4-Diphenylmethylidene-NN-dimethylpiperidinium methyl sulphate.

Atropine-like actions and also has some ganglionic blocking effect.  
No advantage over atropine. Absorbed with some difficulty from alimentary tract, but can be given parenterally.

*Dose.* 50-200 mg. orally.

15-25 mg. subcutaneously or intravenously.

### **Eucatropine Hydrochloride**

A white granular powder, soluble in water; used as a mydriatic.

*Dose.* 2-3 drops of a 5 or 10 per cent solution instilled into the eye.

### **Penthienate Bromide**

("Monodral.")

Diethylmethyl[2-(2-cyclopentyl-2-thien-2'-ylglycolloxy)ethyl] ammonium bromide.

About half the potency of atropine. Can be used as a mydriatic (2 per cent); effect lasts 2 days.

*Dose.* 5-10 mg.

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### Propantheline Bromide

("Probanthine.")

2-Diisopropylaminoethyl xanthen-9-carboxylate methobromide.

Used almost exclusively as spasmolytic in disorders of alimentary tract.

*Dose.* 15-30 mg.

### Tricyclamol Chloride

("Elorine Chloride," "Lergine".)

( $\pm$ )-N-(3-cyclohexyl-3-hydroxy-3-phenyl-propyl)-N-methyl-pyrrolidinium chloride.

Produces the peripheral effects of atropine. Used as an anticholinergic in diseases of alimentary tract.

*Dose.* 50-100 mg.

### Oxyphenonium Bromide

2-Diethylaminoethyl- $\alpha$ -cyclohexyl- $\alpha$ -phenylglycollate methobromide.

Atropine-like effects and may be used as spasmolytic in peptic ulcer. Weaker than atropine. A Tablet contains 5 mg.

*Dose.* 5 mg.

## SYMPATHOMIMETIC DRUGS

### Adrenaline

Epinephrine.

(-)-1-(3:4-Dihydroxyphenyl)-2-methylaminoethanol.

Prepared from an acid extract of the suprarenal glands of animals or synthetically. A light brown or white microcrystalline powder. Very slightly soluble in water; neutral or alkaline solutions readily oxidise and turn pink. Combines with acids to form salts which are readily soluble in water.

#### ADRENALINE INJECTION

0.18 per cent of Adrenaline Acid Tartrate in Water for Injection.

*Dose.* 0.2-0.5 ml. by subcutaneous injection.



### **Noradrenaline Acid Tartrate**

Levarterenol Bitartrate—the monohydrate of (—)-2-amino-1-(3:4-dihydroxyphenyl)ethanol acid tartrate.

*Dose.* By intravenous infusion, to correct arterial hypotension: 5-25 micrograms per minute according to the patient's needs and the response obtained.

### **Isoprenaline Sulphate**

Isopropylnoradrenaline sulphate ("Neo-epinine").

*Dose.* 5-20 mg.

The Tablets—for *sublingual* administration—contain 10 or 20 mg. A Spray (all-glass atomiser) for inhalation to abort asthma at the onset: 1 per cent solution and may contain other spasmolytics (atropine preparations, papaverine).

*Dose.* Should not exceed 1 ml.

### **Mephentermine Sulphate**

Mephedrine sulphate.

*Naα*-Trimethylphenethylamine sulphate dihydrate.

Local application (0.5 per cent solution) to reduce congestion of nasal mucosa.

In postoperative arterial hypotension up to 50 mg. intravenously (2 minutes for injection) or by slow infusion in 5 per cent dextrose solution.

Given orally (5-20 mg.) to combat mental depression and apathy: indications and dangers similar to those of amphetamine.

### **Methoxamine Hydrochloride**

2-Amino-1-(2:5-dimethoxyphenyl)propan-1-ol hydrochloride.

Peripheral vasoconstriction but minimal stimulation of CNS. Slow administration intravenously in hypotensive states—post-operative and in severe myocardial infarction.

*Dose.* 5-10 mg. intravenously and 5-20 mg. intramuscularly.

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### **Methoxyphenamine Hydrochloride**

2-Methoxy-N $\alpha$ -dimethylphenethylamine hydrochloride.

Ephedrine-like action but bronchodilatation is accompanied by minimal pressor effects and only slight cerebral stimulation.

### **Cyclopentamine Hydrochloride**

Cyclopentadrin hydrochloride (Clopane hydrochloride).

Methyl(1-methyl-2-cyclopentylethyl)amine hydrochloride.

Pressor effects of ephedrine, but without conspicuous stimulating action on brain.

*Dose.* 5–10 mg. by slow intravenous injection; 25 mg. intramuscularly.

### **Naphazoline Hydrochloride**

2-(Naphth-1-ylmethyl)iminazoline hydrochloride.

Powerful vasoconstrictor used in a 1 in 2,000 aqueous isotonic solution for relief of nasal congestion.

### **Phenylpropanolamine Hydrochloride**

Norephedrine.

2-Amino-1-phenylpropan-1-ol hydrochloride.

Predominantly a vasoconstrictor, with comparatively weak effects on the bronchi and on the higher cerebral centres.

*Dose.* 25–50 mg.

### **Phenylephrine Hydrochloride**

(—)-1-(3-Hydroxyphenyl)-2-methylaminoethanol hydrochloride.

Used as a spasmolytic in asthma.

It may be given in “expectorant” mixtures, by inhalation, or as a decongestant solution locally in the nose.

*Dose.* 5–10 mg. subcutaneously or intramuscularly.

## **Methylamphetamine**

*d*-Deoxyephedrine.

(+)-*N* $\alpha$ -Dimethylphenethylamine.  $C_{10}H_{15}N$ .

A clear, colourless, volatile liquid with a characteristic odour resembling geranium leaves.

Used as an inhalant for nasal congestion (special inhaler).

## **Methylamphetamine Hydrochloride**

$C_{10}H_{15}N, HCl$ .

*Dose.* 2.5–10 mg. orally (as Tablets).

10–30 mg. intramuscularly or intravenously as an analeptic.

## **Hydroxyamphetamine Hydrobromide**

("Paredrinex.")

4-(2-Aminopropyl)phenol hydrobromide.

1 per cent solution, as a spray, to reduce congestion of the nasal mucosa: 5–10 mg. intravenously or 10–20 mg. intramuscularly to maintain blood pressure during spinal anaesthesia.

## **Phenmetrazine Hydrochloride**

("Preludin.")

3-Methyl-2-phenylmorpholine hydrochloride.  $C_{11}H_{15}ON, HCl$ .

Therapeutically, an amphetamine-like substance which may reduce appetite and cause few side-effects on cardiovascular system. Like amphetamine group of drugs it is an ancillary to strict dieting in the management of obesity.

*Dose.* 25 mg.

## **Pipradol Hydrochloride**

("Meratran.")

$\alpha$ -Diphenylpiperid-2-ylmethanol hydrochloride.

CNS stimulant. Action resembles that of amphetamine; but it is not a sympathomimetic amine, and has only slight effects on heart and blood pressure. Relieves drowsiness without causing euphoria.

## ADRENOLYTIC DRUGS

### **Phenoxybenzamine**

("Dibenyline.")

Benzyl-2-chloroethyl(1-methyl-2-phenoxyethyl)amine hydrochloride.

Capsules containing 10 mg. in each are available.

*Dose.* Up to 240 mg. daily in divided doses: 0.5–2 mg. per kg. body weight diluted in 250–500 ml. of sterile normal saline or 5 per cent dextrose solution.

Given by slow intravenous infusion (1 hour).

### **Dihydroergotamine**

Ergotamine-like substance: hydrogenation increases the sympatholytic effect and diminishes oxytocic and pressor effects. Used in migraine.

*Dose.* As the methanesulphonate or tartrate 0.25–1 mg. subcutaneously, intramuscularly or intravenously; 2–4 mg. by mouth in solution.

### **Phentolamine Hydrochloride**

2-(N-3-Hydroxyphenyl-4-toluidinomethyl)iminazoline hydrochloride.

Powerful adrenolytic and sympatholytic effect resulting in vasodilatation and hypotension.

Limited therapeutic applications; rarely used except in diagnosis of phæochromocytoma. Action of phentolamine is reversed by noradrenaline.

*Dose.* 50–100 mg.

### **Phentolamine Methanesulphonate**

Actions and uses those of Phentolamine Hydrochloride, but the methanesulphonate is given parenterally in diagnostic procedures and in management of patients before, during and after operation for phæochromocytoma.

### **Piperoxane Hydrochloride**

Benzodioxane Hydrochloride.

2-Piperidinomethylbenzo-1:4-dioxan hydrochloride

$C_{14}H_{19}O_2N, HCl$ .

A white crystalline powder with a bitter acid taste.

*Dose.* 10–20 mg. intravenously.

Adrenolytic effect much greater than sympatholytic action, and therefore administration sometimes useful in diagnosis of chromaffin tumours.

### **Tolazoline Hydrochloride**

Benzazoline Hydrochloride ("Priscol").

2-Benzyliminazoline hydrochloride.

Sympatholytic action (weak adrenolytic) with significant effects on peripheral blood flow. Used in peripheral vascular disease with disabilities attributable to ischaemia of tissues.

*Dose.* 25–50 mg. by mouth.

10–20 mg. by injection.

## **GANGLIONIC BLOCKING AGENTS**

### **Hexamethonium Tartrate**

Hexamethylenebistrimethylammonium di(hydrogen tartrate).

A white or creamy-white, hygroscopic powder with an acid taste; soluble 1 in 0.7 of water.

#### **HEXAMETHONIUM TARTRATE INJECTION**

A sterile solution in Water for Injection, adjusted to pH 7.0.

Vials containing 138 mg. in 1 ml. are available.

#### **HEXAMETHONIUM TARTRATE TABLETS**

Tablets containing 350 mg. are available.

*Doses.* Determined by the physician according to the needs of the patient. See text.

### **Pentamethonium**

### **Tetraethylammonium**

} See text.

## FORMULARY

### **Pentolinium Tartrate**

Pentamethylenebis(1-methylpyrrolidinium hydrogen tartrate).

A white to light cream-coloured crystalline powder, very soluble in water.

#### **PENTOLINIUM TABLETS**

Tablets containing 10, 40 and 200 mg. are available.

#### **PENTOLINIUM INJECTION**

Multi-dose vials containing solutions of 0.5 per cent and 2.5 per cent are available.

*Doses.* Determined by the physician according to the needs of the patient. See text.

### **Chlorisondamine Chloride**

("Ecolid.")

Ethylene-1-(4:5:6:7-tetrachloro-2-methylisoindolinium)-2-trimethylammonium dichloride.

Available as Tablets of 25 mg. and 50 mg. and as vials of 5 mg.

*Dose.* Determined by the physician according to the needs of the patient.

### **Mecamylamine Hydrochloride**

("Inversine.")

3-Methylaminoisocamphane hydrochloride.

A white, crystalline powder; soluble 1 in 5 of water. Available as Tablets of 2.5 mg. and 10 mg.

*Dose.* Determined by the physician according to the needs of the patient.

### **Pempidine Tartrate**

("Perolysen.")

Available as Tablets of 1 mg., 5 mg. and 10 mg.

*Dose.* Determined by the physician according to the needs of the patient.

**Pentacynium Methylsulphate**

("Presidal.")

Available as tablets of 100 mg. and as an Injection containing 25 mg. per ml.

*Dose.* Determined by the physician according to the needs of the patient.

**Trimetaphan Camphorsulphonate**

A white, crystalline powder with a very slight odour and a bitter taste; soluble 1 in less than 5 of water.

Available as a dry powder in vials of 250 mg.

Administered by intravenous infusion in a strength of 1 mg. per ml.

*Dose.* Determined by the physician according to the needs of the patient.

**DRUGS ACTING ON THE NERVOUS SYSTEM**

**(other than Autonomic Nervous System)**

(see Chapter 7)

**LOCAL ANÆSTHETICS**

**PREPARATIONS MAINLY FOR**

**TOPICAL APPLICATION**

**Cocaine**

Methyl benzoylecgonine, an alkaloid obtained from leaves of *Erythroxylum coca* or by synthesis. Colourless crystals. Physical properties those of alkaloids (q.v.). Almost insoluble in water.

**COCAINE HYDROCHLORIDE**

Colourless crystals, *freely soluble in water* to make preparations for surface anæsthesia.

*Dose.* 8–16 mg.

## FORMULARY

### **Amethocaine Hydrochloride**

The hydrochloride of the *p-n*-butylaminobenzoic ester of 2-dimethylaminoethanol. White crystalline powder, soluble in water. Surface anæsthesia 0.5–2 per cent. Infiltration anæsthesia 0.03–0.1 per cent. Nerve block 0.1 per cent. Spinal block 0.1–0.5 per cent. Eye-drops 1 per cent.

### **Benzocaine**

Ethyl *p*-aminobenzoate. White crystalline powder, almost insoluble in water. Used in dusting powder (5–20 per cent), ointment (10 per cent), and lozenge (97.2 mg.).

**Lignocaine Hydrochloride**—see below.

## PREPARATIONS FOR INFILTRATION

### **Procaine Hydrochloride**

The hydrochloride of 2-diethylaminoethyl *p*-aminobenzoate. Colourless crystalline powder. Freely soluble in water. Infiltration 0.5–2 per cent. Nerve block 2 per cent. Spinal block 2–5 per cent (up to 150 mg.)

#### PROCAINE AND ADRENALINE INJECTION

Procaine Hydrochloride 2 per cent and Adrenaline 1 in 50,000.

For infiltration (skin); adrenaline causes ischæmia and delays absorption of procaine.

### **Lignocaine Hydrochloride**

The monohydrate of the hydrochloride of diethylaminoacet-2:6-xylidide. A white crystalline powder, freely soluble in water. Preparations and concentrations—as for Procaine Hydrochloride. *N.B.* Lignocaine also produces surface anæsthesia as 1–2 per cent solution.

#### LIGNOCAINE AND ADRENALINE INJECTION

2 per cent with adrenaline 1 in 60,000.

Uses and preparations—see Procaine and Adrenaline Injection.



### **Cinchocaine Hydrochloride**

The hydrochloride of the 2-diethylaminoethylamide of 2-butoxy-cinchonic acid. A white crystalline powder freely soluble in water. Infiltration 0.03-0.1 per cent. Nerve block 0.1 per cent. Spinal block 0.1-0.5 per cent.

## **CENTRAL NERVOUS SYSTEM STIMULANTS**

### **Caffeine**

1:3:7-Trimethylxanthine. An alkaloid obtained from tea or coffee or prepared synthetically. White powder, freely soluble in hot water.

*Dose.* 300-600 mg.

### **Amphetamine**

Racemic desoxynorephedrine. ( $\pm$ )-2-Aminopropylbenzene. A colourless liquid with a characteristic odour and taste. Slightly soluble in water; readily soluble in various organic solvents. Administered by inhalation (from specially constructed inhalers) to produce local vasoconstriction.

### **Amphetamine Sulphate**

A white powder, soluble in water.

*Dose.* 5-10 mg.

#### **AMPHETAMINE SULPHATE TABLETS**

Usual strength 5 mg. in a tablet.

### **Dexamphetamine Sulphate**

("Dexedrine.")

The dextro-isomer of amphetamine, and has about twice the activity of the racemic compound.

*Dose.* 5-10 mg.

#### **DEXAMPHETAMINE SULPHATE TABLETS**

Usual strength 5 mg. in a tablet.

### Nikethamide

Pyridine-3-carboxydiethylamide. A yellowish, oily liquid or crystalline solid, miscible with water.

*Dose.* 0.25-1 G. parenterally. Ineffective by mouth.

#### NIKETHAMIDE INJECTION

25 per cent solution; 1-4 ml. intravenously.

### Leptazol

1:5-Pentamethylenetetrazole. Colourless crystals or white powder.

*Dose.* 50-100 mg. parenterally.

#### LEPTAZOL INJECTION

10 per cent solution; analeptic dose 100 mg. intravenously; but up to 500 mg. in barbiturate poisoning.

### Picrotoxin

Active principle of *Anamirta cocculus*. A crystalline substance with a very bitter taste.

*Dose.* 3-6 mg. intravenously as the Injection.

#### PICROTOXIN INJECTION

0.1 per cent solution given intravenously as an analeptic in barbiturate poisoning (obsolescent).

### Bemegride

$\beta$ -Ethyl- $\beta$ -methylglutarimide. A colourless crystalline powder readily soluble in hot water. Used as an analeptic in barbiturate poisoning. Inject intravenously (0.5 per cent solution); 50 mg. repeated at intervals of 5 minutes according to patient's needs.

### Amiphenazole Hydrochloride

("Daptazole.")

2:4-Diamino-5-phenylthiazole hydrochloride.

A whitish powder freely soluble in hot water.

*Dose.* Depends on needs of patient. Used as an analeptic in barbiturate poisoning and as a non-specific stimulant of the respiratory centre. The *Injection* is available in vials containing 30 mg. and 150 mg.

### **Strychnine Hydrochloride**

The hydrochloride of strychnine—an alkaloid obtained from the seeds of various species of *Strychnos*. The salt is soluble in water; intensely bitter.

*Dose.* 2-8 mg. A drug of pharmacological interest, but now rarely used therapeutically.

## **CENTRAL NERVOUS SYSTEM DEPRESSANTS**

### **ALCOHOLS**

#### **Alcohol**

is Ethyl Alcohol or Ethanol; strength 95 per cent

Various dilutions are available.

*Rectified Spirit* is 90 per cent alcohol.

*Proof Spirit* contains about 57.1 v/v  $C_2H_6O$ .

Whisky, Brandy and Rum all contain about 40 per cent v/v alcohol.

#### **Methyl Alcohol**

Methanol. Used in industry. Highly poisonous: serious metabolic and neurological complications in man.

#### **Industrial Methylated Spirit**

Ethanol with wood naphtha (5 per cent).

## **GENERAL ANÆSTHETICS**

#### **Anæsthetic Ether**

Diethyl Ether.

Highly volatile (b.p.  $34^{\circ}C.$ ); characteristic odour; inflammable and explosive. Protect from light.

#### **Vinyl Ether**

Divinyl Ether.

B.p.  $28^{\circ}C$ . Physical properties resemble those of Diethyl Ether.

## FORMULARY

### **Ethyl Chloride**

B.p.  $12.5^{\circ}\text{C}$ . Supplied in glass tube with special nozzle for spraying. Characteristic odour. Inflammable.

### **Chloroform**

Volatile. Characteristic odour. Not inflammable. Protect from light.

### **Trichloroethylene**

B.p.  $86^{\circ}\text{C}$ . Chloroform-like odour. Blue colouring matter may be added. Protect from light.

### **Cyclopropane**

Colourless inflammable gas; supplied compressed in cylinders.

### **Nitrous Oxide**

Laughing Gas.

Colourless gas. Characteristic odour. It supports combustion.

### **Halothane**

2-Bromo-2-chloro-1:1:1-trifluoroethane. A clear, colourless liquid. Non-inflammable. Chloroform-like odour. Protect from light and moisture.

## HYPNOTICS

### **1. The Barbiturates**

#### *(a) Short hypnotic effect*

**Cyclobarbitone**; 200–400 mg.

The Tablet contains 180 mg.

**Hexobarbitone**; 250–500 mg.

The Tablet contains 240 mg. (The *sodium salt* is given intravenously as a basal anæsthetic.)

**\*Quinalbarbitone Sodium**; 50–200 mg.

The Capsule contains 50 mg. or 100 mg.

Tablets also available (see footnote, p. 694).

(b) *Intermediate hypnotic effect*

**Amylobarbitone**; 100–200 mg.

The Tablet contains 50 or 100 mg.

**Butobarbitone**; 100–200 mg.

The Tablet contains 100 mg.

**\*Pentobarbitone Sodium**; 100–200 mg.

Capsules and Tablets of various strengths available.

(c) *Prolonged hypnotic effect*

**Barbitone Sodium**; 300–600 mg.

**Phenobarbitone**; 30–120 mg.

Both preparations are available as Tablets.

Their prolonged action and subsequent drowsiness are rarely required.

2. **Other Hypnotics**

**Glutethimide**; 250–500 mg. (Tablets).

Equivalent to Pentobarbitone in potency.

**Chloral Hydrate**; 0.3–2 G. (adults).

Aqueous solution well diluted and flavoured.

**Carbromal**; 0.3–1 G. (Tablets).

Relatively weak.

**Paraldehyde**; 2–8 ml. orally (in brandy) or 5 ml. intramuscularly.

Special indications (see text).

**Methylpentynol**; 0.25–1 G. (Capsules).

A weak hypnotic.

**Alcohol**—usually given as whisky or brandy.

\* These two representative drugs suffice for most purposes in practice.

## THE TRANQUILLISERS

### **Chlorpromazine Hydrochloride**

2-Chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

*Dose.* 75-150 mg. daily in divided doses.

The Tablet contains 10, 25, 100, or 200 mg.

An Injection contains 25 mg. per ml.

### **Meprobamate**

2:2-Di(carbamoyloxymethyl)pentane.

*Dose.* 400 mg.

The Tablet contains 400 mg.

### **Benactyzine Hydrochloride**

2-Diethylaminoethyl benzilate hydrochloride.

*Dose.* 1-4 mg.

A Tablet contains 1 mg.

### **Hydroxyzine Hydrochloride**

1-(*p*-Chlorodiphenylmethyl)-4-[2-(2-hydroxyethoxy)ethyl]-piperazine dihydrochloride.

*Dose.* 10-25 mg.

A Tablet contains 10 mg.

A Syrup contains 2 mg. per ml.

### **Methylpentynol**—see Hypnotics

### **Reserpine**

An alkaloid from the roots of *Rauwolfia serpentina*.

*Dose.* 0.25-1 mg. daily. See text.

A Tablet contains 0.25 mg.

Various pharmaceutical preparations of *Rauwolfia* alkaloids are available.

## ANTICONVULSANT DRUGS

### Phenobarbitone

5-Ethyl-5-phenylbarbituric Acid.

A white powder only slightly soluble in water (cf. Sodium salt).

*Dose.* 30-120 mg. Available in Tablets and in various other preparations.

#### PHENOBARBITONE SODIUM

Is soluble and can be injected parenterally.

### Phenytoin Sodium

Sodium diphenylhydantoin. A white powder, hygroscopic and dispensed in Capsules.

*Dose.* 50 100 mg.

### Methoin

5-Ethyl-3-methyl-5-phenylhydantoin.

A colourless powder; insoluble in water; dispensed in Tablets.

A Tablet contains 100 mg.

*Dose.* 50 100 mg.

### Troxidone

3:5:5-Trimethyloxazolidine-2:4-dione.

Colourless crystals dispensed in capsules.

*Dose.* 1-2 G. daily in divided doses.

### Bromides

Sodium and potassium bromides have been used as anticonvulsants but they are virtually obsolete.

## RELAXANTS OF VOLUNTARY MUSCLE

### Tubocurarine Chloride

The chloride of an alkaloid (+)-tubocurarine obtained from stems of plants of genus *Chondodendron*. Chemical structure complex (see BP). White, odourless powder. Soluble in warm water.

*Dose.* Depends on patient's requirements (see text).

#### TUBOCURARINE INJECTION

A solution (1 per cent) of the above in Water for Injection.

### Gallamine Triethiodide

1:2:3-tri(2-Diethylaminoethoxy)benzene triethiodide.

A whitish powder, freely soluble in water.

*Dose.* Depends on patient's requirements (see text).

#### GALLAMINE INJECTION

Gallamine Triethiodide is dissolved in Water for Injection: amount of drug is stated on label.

### Suxamethonium Chloride

The dihydrate of bis-2-dimethylaminoethyl succinate bismethochloride. A whitish powder freely soluble in water.

*Dose.* Depends on patient's needs.

#### SUXAMETHONIUM CHLORIDE INJECTION

A sterile solution made up with Water for Injection: usual strength 50 mg. in 1 ml.

## DRUGS USED IN PARKINSONISM

The chemical composition of these drugs and their doses are mentioned in the text.

### Mephenesin

### Benzhexol Hydrochloride



**Diethazine Hydrochloride**

**Caramiphen Hydrochloride**

**Ethopropazine Hydrochloride**

**"Disipal"**

## **ANALGESICS**

(see Chapter 8)

### **OPIUM AND RELATED ANALGESICS**

#### **Opium**

The dried juice obtained by incision from the unripe capsules of the opium poppy—*Papaver somniferum*. Dark brown—almost black—masses with characteristic odour. Contains a large number of alkaloids: principal alkaloid is *morphine* (see text).

#### **Powdered Opium**

Opium standardised to contain 10 per cent of *morphine*. Numerous pharmaceutical preparations of opium (see BPC and EP).

##### **OPIUM TINCTURE**

Laudanum, 1 per cent morphine.

*Dose.* 0.3–2 ml.

##### **CAMPHORATED OPIUM TINCTURE**

Paregoric, 0.05 per cent morphine.

*Dose.* 2–8 ml.

##### **POWDER OF IPECACUANHA AND OPIUM**

Dover's Powder: 10 per cent opium.

*Dose.* 300–600 mg.

##### **AROMATIC POWDER OF CHALK WITH OPIUM**

Opium 2.5 per cent.

*Dose.* 0.6–4 G.

## FORMULARY

### **Morphine Hydrochloride**

The usual physical properties of alkaloidal salts.

*Dose.* 8–20 mg.

The sulphate and tartrate are also available and have the same dose.

See BPC or EP for numerous examples of preparations of morphine salts for oral and parenteral administration.

### **Papaveretum**

The hydrochlorides of alkaloids of opium. Contains about 50 per cent morphine. Comparisons with morphine must be based on dosage expressed in terms of morphine content.

*Dose.* 10–20 mg.

### **Codeine**

The 3-methyl ether of morphine.

### **Codeine Phosphate**

The alkaloidal salt is soluble in water and used in various pharmaceutical preparations. A very weak cough suppressant and a poor analgesic, but causes constipation. An expensive preparation.

### **Diamorphine Hydrochloride**

Diacetylmorphine Hydrochloride. Heroin Hydrochloride. Freely soluble in water.

*Dose.* 5–10 mg.

Various preparations for oral administration are available (Elixir, Linctus, Glycerin).

Not official. *Caution*—a drug of addiction.

### **Pethidine Hydrochloride**

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. A colourless crystalline powder, freely soluble in water.

*Dose.* 25–100 mg. by mouth or intramuscularly.

25–50 mg. intravenously.

**Methadone Hydrochloride**

Is the hydrochloride of ( $\pm$ )-2-dimethylamino-4:4-diphenylheptan-5-one.

Freely soluble in glycerin; less soluble in water.

*Dose.* 5-10 mg.

Injection is given subcutaneously.

**Papaverine Hydrochloride**

An alkaloid of opium. It has no hypnotic or analgesic action. See text.

*Dose.* 150-300 mg.

**Nalorphine Hydrobromide**

N-Allylnormorphine hydrobromide.

Antagonises most of the characteristic actions of morphine and drugs which have a similar pharmacological action.

*Dose.* 5-10 mg. (usually intravenously) up to a total of 40 mg. in severe cases of poisoning.

**SALICYLATES AND OTHER ANALGESICS**

**Salicylic Acid**—see below

**Acetylsalicylic Acid**

Aspirin. Very sparingly soluble in water. Characteristic taste.

*Dose.* 0.3-1 G.

The Tablet contains 0.3 G.

Various compound preparations of Aspirin, Phenacetin and Caffeine are available as analgesics (Capsules, Elixirs, Mixtures, Tablets); and Codeine is often used instead of Caffeine.

**Soluble Acetylsalicylic Acid Tablets**

Soluble Aspirin.

Less liable than aspirin to cause gastric irritation.

*Dose.* 0.3-1 G.

The Tablet contains 0.3 G.

### **Sodium Salicylate**

A white powder, freely soluble in water; unpleasant sweetish taste.

*Dose.* 0.6–2 G.

Used as analgesic only in acute and subacute rheumatic fever.

### **Methyl Salicylate**

A colourless or pale yellow liquid with characteristic aromatic odour and taste. Used almost exclusively as a *counter-irritant* (25 per cent in arachis oil); partly absorbed through the skin.

### **Salicylic Acid**

*o*-Hydroxybenzoic acid. Colourless crystals, almost insoluble in cold water, but freely soluble in alcohol and in glycerin. On mucous membranes it is an irritant, and is rarely given orally; on skin it is keratolytic (utilised in various dermatoses).

### **Phenacetin**

Aceto-*p*-phenetidin.

*N-p*-Ethoxyphenylacetamide. A white crystalline powder almost insoluble in water. Rarely prescribed alone but as adjuvant to aspirin in compound analgesic powders.

*Dose.* 0.3–0.6 G.

### **Paracetamol**

*p*-Acetamidophenol ("Panadol").

For relationship to Phenacetin—see text.

*Dose.* 500 mg., dispensed in Tablets.

### **Phenylbutazone**

("Butazolidin.")

4-*n*-Butyl-1:2-diphenylpyrazolidine-3:5-dione.

*Dose.* 200–400 mg. daily in divided doses.

Tablets containing 100 mg. available.

Analgesic effect in certain types of chronic rheumatic disease, in gout, and in thrombophlebitis.

Wide variety of toxic effects (see text).

**Phenazone**

**Acetanilide**

**Amidopyrine**

} Potent analgesics but rarely used  
because of toxic effects.

## DRUGS USED IN GOUT ..

### **Cinchophen**

2-Phenylquinoline-4-carboxylic acid or Phenylcinchoninic Acid.

Whitish crystals sparingly soluble in water.

Analgesic antipyretic; pharmacological and toxicological effects resemble those of salicylates; used almost exclusively in gout. Risk of hepatitis.

### **Colchicine**

An alkaloid from corm and seeds of *Colchicum autumnale*.

*Dose.* 1 mg. Its use as an analgesic is restricted to cases of gout.

### **Probenicid**

*p*-(Di-*n*-propylsulphamoyl)benzoic acid.

4-Dipropylsulphamoylbenzoic acid.

Inhibits reabsorption of urate by renal tubules and increases the excretion of uric acid. Used in treatment of gout, but benefits result indirectly rather than by true analgesic action.

## HISTAMINE AND ANTIHISTAMINES

(see Chapter 9)

### **Histamine Acid Phosphate**

The di-acid phosphate of histamine, 4-2'-aminoethyliminazole. Colourless crystals, soluble in water.

*Dose.* 0.5-1 mg. by subcutaneous injection.

#### HISTAMINE ACID PHOSPHATE INJECTION

A sterile solution in Water for Injection: 1 ml. contains 1 mg.

## FORMULARY

### **Antazoline Hydrochloride**

2-(N-Benzylanilinomethyl)iminazoline hydrochloride.

Feathery crystals, slightly soluble in water.

*Dose.* 100–200 mg.

#### ANTAZOLINE TABLETS

A Tablet contains 100 mg.

#### ANTAZOLINE CREAM

Contains 2 per cent Antazoline

#### ANTAZOLINE COMPOUND EYE-DROPS BNF

Contain 0.5 per cent Antazoline.

### **Cyclizine Hydrochloride**

1-Diphenylmethyl-4-methylpiperazine hydrochloride.

A white crystalline powder, sparingly soluble in water.

*Dose.* 25–50 mg.

#### CYCLIZINE TABLETS BNF

A Tablet contains 50 mg.

### **Diphenhydramine Hydrochloride**

2-Diphenylmethoxyethyl-dimethylamine hydrochloride.

A white crystalline powder, soluble in water; protect from light.

*Dose.* 25–75 mg.

#### DIPHENHYDRAMINE CAPSULES

A Capsule contains 25 or 50 mg. according to the requirement of the prescriber.

#### “BENADRYL PARENTERAL.”

1 ml. contains 10 mg. In emergency 10–50 mg. may be given by intravenous injection.

### **Meclozine Hydrochloride**

1-(*p*-chlorobenzhydryl)-4-(*m*-methylbenzyl)piperazine dihydrochloride.

A white powder, slightly soluble in water.

*Dose.* 25–50 mg.

## DILLING'S CLINICAL PHARMACOLOGY

### MECLOZINE TABLETS

A Tablet contains 25 mg.

### Mepyramine Maleate

N-*p*-Methoxybenzyl-N'N'-dimethyl-N-2-pyridylethylenediamine hydrogen maleate.

A white powder, soluble in water, forming an acid solution.

*Dose.* 300–800 mg. daily, in divided doses.

### MEPYRAMINE TABLETS

The strength to be dispensed must be stated.

### Promethazine Hydrochloride

10-(2-Dimethylaminopropyl)phenothiazine hydrochloride.

A yellowish-white powder; protect from light and moisture.

*Dose.* 25–75 mg. daily.

### PROMETHAZINE HYDROCHLORIDE TABLETS

The strength to be dispensed must be stated.

## DRUGS ACTING MAINLY ON THE HEART

(see Chapter 10)

### Digitalis Leaf

The dried leaves of *Digitalis purpurea*.

Contains numerous glycosides including digitoxin, gitoxin and gitalin.

Aqueous preparations are unstable and are not recommended.

### PREPARED DIGITALIS

A standardised preparation of powdered Digitalis Leaf. Biologically assayed: adjusted to contain 1 Unit in 100 mg.

*Dose.* 30–100 mg. The official Tablet contains 60 mg.

### DIGITALIS TINCTURE

Not recommended as its potency diminishes when dispensed in aqueous mixtures.

*Dose.* 0.3–1 ml.

## FORMULARY

### Digoxin

A glycoside obtained from the leaves of *Digitalis lanata*.

*Dose.* 1–1.5 mg. orally, or 0.5–1 mg. intravenously initially; 0.25 mg. once or twice daily orally for maintenance. The official Tablet contains 0.25 mg.

#### DIGOXIN INJECTION

Contains 1 mg. Digoxin in 20 ml. of solution, and is used immediately after preparation.

### Ouabain

A crystalline glycoside obtained from the seeds of *Strophanthus gratus*.

*Dose.* 0.12–0.25 mg. intravenously.

*N.B.* Potency of Ouabain (or Strophanthin-G) is about twice that of Strophanthin-K.

### Quinidine Sulphate

Quinidine is a dextrorotatory stereo-isomer of quinine and is obtained from the bark of species of *Cinchona*. The sulphate of quinidine is used therapeutically.

*Dose.* 60–300 mg. (adjusted to the needs of the patient—see text).

### Procainamide Hydrochloride

4-Amino-N-(2-diethylaminoethyl)benzamide hydrochloride.

Freely soluble in water.

*Dose.* 0.5–1 G. orally. The Tablet contains 250 mg.

100–500 mg. by *slow* intravenous injection as a 2.5 per cent solution (see text).

## VASODILATORS AND HYPOTENSIVE AGENTS

### Glyceryl Trinitrate

Trinitrin; Nitroglycerol.  $C_3H_5(O.NO_2)_3$ .

An oily liquid with an aromatic taste.

Explodes on rapid heating or percussion.



## DILLING'S CLINICAL PHARMACOLOGY

### GLYCERYL TRINITRATE TABLETS

A Tablet contains 0.5 mg.

Chewed slowly before swallowing (absorption mainly by buccal mucosa).

Tablet base may be chocolate or mannitol.

Other Nitrites include AMYL NITRITE—dispensed in vitrellæ and given by inhalation; and PENTAERYTHRITOL TETRANITRATE given orally as a Tablet diluted with Lactose (10–20 mg. thrice daily). These and other nitrites have few therapeutic advantages over Glyceryl Trinitrate; and Amyl Nitrite has disagreeable side-effects.

### Khellin

Visammin. A bitter, crystalline substance obtained from *Ammi visnaga* fruit.

Dose. 25–100 mg.

### Veratrum

The rhizome and roots of *Veratrum viride*.

Action depends on the alkaloids protoveratrine A and protoveratrine B. Various proprietary preparations of Veratrum contain these alkaloids (see text).

### Rauwolfia

The dried root of *Rauwolfia serpentina*. Contains numerous alkaloids: the most important is reserpine. Powdered whole root may be used therapeutically or preparations containing one or more of the alkaloids.

### Reserpine

See above.

Dose. 0.25–1 mg. daily in arterial hypertension (as an adjuvant to other hypotensive agents—see text). Similar doses are used in mild psychotic illness as a tranquilliser, but up to 10 mg. daily may be needed in severe cases at outset.

## FORMULARY

### **Hydrallazine Hydrochloride**

1-Hydrazinophthalazine hydrochloride.

*Dose.* About 100 mg. may be used as a hypotensive agent in conjunction with reserpine (see text).

## DRUGS ACTING ON RESPIRATORY SYSTEM

(see Chapter 11)

### EXPECTORANTS

#### **Potassium Iodide**

Colourless crystals or white powder, soluble in water, slightly bitter saline taste. Incompatible with alkaloidal salts.

*Dose.* 0.3–2 G. (as expectorant usually 0.3–0.6 G.).

#### **Sodium Iodide**

Physical properties and dose similar to those of Potassium Iodide.

#### **Ammonium Chloride**

#### **Ammonium Bicarbonate**

#### **Ipecacuanha Tincture**

} See text.

#### **Sodium Chloride Compound Mixture**

A solution of Sodium Chloride and Sodium Bicarbonate flavoured with anise and chloroform.

*Dose.* 15–30 ml. in a tumblerful of hot water, sipped slowly.

#### **Benzoin Compound Tincture**

Friars' Balsam.

Prepared from Benzoin, a balsamic resin; agreeable pungent odour.

*Dose.* 2 ml. in 500 ml. of hot water as inhalation.

## DILLING'S CLINICAL PHARMACOLOGY

### BENZOIN INHALATION

Contains Benzoin 10·3 per cent, prepared Storax 6·8 per cent, in industrial methylated spirit.

*Dose.* 4 ml. in 500 ml. of hot water *as inhalation*.

### Menthol Inhalation

Contains Menthol about 2 per cent in industrial methylated spirit.

## COUGH SUPPRESSANTS

### Camphorated Opium Tincture

Paregoric.

Opium Tincture with Benzoic Acid, Anise and Camphor. *Prescribed* as the Undiluted Tincture. *Administered* in warm water: the camphor is precipitated, forming opalescent suspension.

*Dose.* 2-8 ml. taken in 30 ml. water (2 mg. of anhydrous morphine in 4 ml.).

### Diamorphine Linctus

Diamorphine is synonymous with Diacetylmorphine or Heroin.

*Dose.* 2-8 ml. (4 ml. contains 3 mg. of diamorphine hydrochloride).

### Methadone Linctus

Methadone is ( $\pm$ )-2-dimethylamino-4:4-diphenylheptan-5-one hydrochloride. Contra-indicated in pregnancy and for young children.

*Dose.* 4 ml. (contains 2 mg. methadone hydrochloride).

### Pholcodine Linctus

Pholcodine is morpholinylethylmorphine.

*Dose.* 4-8 ml. (4 ml. containing 4 mg. pholcodine).

### Pholcodine Citrate Syrup

*Dose.* 2-4 ml. (4 ml. contains 8 mg. of pholcodine).

### Codeine Phosphate

A weak cough suppressant, inferior to pholcodine (see text).

Various preparations available (Tablet, Linctus, Syrup).

## FORMULARY

### SPASMOLYTIC DRUGS

#### **Adrenaline Injection**

Adrenaline Tartrate Injection contains the equivalent of 0.1 per cent w/v of adrenaline suitably prepared.

*Dose.* 0.2–0.5 ml., by subcutaneous injection.

Keep in small, well-filled containers, protected from light.

#### **Non-official Adrenaline Spray**

There is no official preparation of 1 per cent adrenaline for inhalation, but adrenaline hydrochloride can be substituted for isoprenaline sulphate in the formula of Spray of Isoprenaline Sulphate, thus:

Adrenaline hydrochloride	0.5 G.
Propylene glycol	2.5 ml.
Sodium metabisulphite	0.05 G.
Distilled water to	50 ml.

Keep in small, well-filled containers, protected from light.

#### **Adrenaline and Atropine Compound Spray**

Adrenaline 0.46 per cent, atropine methonitrate 0.116 per cent and papaverine hydrochloride 0.8 per cent, suitably dispensed in distilled water. Keep in small, well-filled containers, protected from light.

#### **Ephedrine Hydrochloride Tablets**

*Dose.* 16–60 mg.

A Tablet contains 30 mg.

#### **Isoprenaline Tablets**

Isoprenaline Sulphate Tablets, Isopropylnoradrenaline.

*Dose.* 5–10 mg.

A Tablet contains 10 mg. Dissolve under the tongue.

### **Isoprenaline Sulphate Spray**

1 per cent w/v Isoprenaline Sulphate.

Keep in small, well-filled containers, protected from light.

### **Isoprenaline Sulphate Compound Spray**

Papaverine hydrochloride 2.5 per cent and atropine methonitrate 0.2 per cent added to Spray of Isoprenaline Sulphate. Keep in small, well-filled containers, protected from light.

### **Aminophylline Injection**

Theophylline with Ethylenediamine Injection. A sterile solution of Aminophylline in Water for Injection free from carbon dioxide.

*Dose.* 0.25–0.5 G., by slow intravenous injection.

Aminophylline Injection contains 0.25 G. in 10 ml.

### **Aminophylline Tablets**

*Dose.* 0.1–0.3 G.

A Tablet contains 100 mg.

Store in airtight container, protected from light.

### **Cortisone Tablets**

Cortisone Acetate Tablets.

*Dose.* 50–300 mg. daily in divided doses.

A Tablet contains 25 mg.

### **Corticotrophin Injection**

A sterile solution of Corticotrophin in Water for Injection.

*Dose.* 10–25 Units every six hours, subcutaneously or intramuscularly.

Store at temperature of 2–4° C.

### **“H.P. Acthar Gel”**

(Proprietary preparation.)

A highly purified preparation of Corticotrophin in a bland gelatin medium containing 20 or 40 Units per ml. for intramuscular use.

**Prednisolone Tablets**

Deltahydrocortisone.

*Dose.* 10–50 mg. daily in divided doses.

A Tablet contains 5 mg.

**Prednisone Tablets**

Deltacortisone.

*Dose.* 10–50 mg. daily in divided doses.

A Tablet contains 5 mg.

**Ipecacuanha and Opium Tablets**

Dover's Powder Tablets.

*Dose.* 0.3–0.6 G.

A Tablet contains 0.3 G.

An obsolescent preparation.

**Oxygen**

O<sub>2</sub>. A colourless, odourless gas.

Stored in metal cylinders, painted black with white shoulders. Supplied to patient by reducing valve, flowmeter and mask or tent. Usually 40–60 per cent concentration in air is adequate, with a flow of 2–8 litres of oxygen/minute.

**Carbon Dioxide**

CO<sub>2</sub>. A colourless, odourless gas, which does not support combustion, and is heavier than air.

Cylinders are painted grey.

Oxygen and Carbon Dioxide Mixtures contain 5–7 per cent CO<sub>2</sub> in oxygen. Cylinders are painted black, with grey and white quartering on shoulders.

**Solid Carbon Dioxide**

(Carbon dioxide snow.)

Formed by escape of carbon dioxide under high compression. Used in the form of a compressed mould or "pencil" as caustic in dermatological practice.

## PHARMACOLOGY OF THE ENDOCRINE GLANDS

(and certain other preparations used in the treatment of  
endocrine disorders)

(see Chapter 12)

### THYROID AND ANTITHYROID DRUGS

#### Thyroid

Prepared from the thyroid glands of oxen, sheep or pigs. It contains 0.1 per cent of iodine as thyroxine. Amorphous powder. Less reliable than Thyroxine Sodium: variation noted in therapeutic potency.

*Dose.* 30-250 mg. daily (see text).

#### THYROID TABLETS

A Tablet contains 30 mg.

#### Thyroxine Sodium

(L-Thyroxine Sodium.)

Synthetic, tasteless, white to pale-buff powder. A completely reliable preparation but expensive by comparison with *Thyroid*.

*Dose.* 0.05-0.5 mg. daily. Available as Tablets.

#### THYROXINE SODIUM TABLETS

A Tablet contains 0.05 mg.

#### Liothyronine

((-)-Triiodothyronine.)

"Tertroxin" is the sodium derivative. Present in minute amounts in the thyroid gland, but probably elaborated in various tissues from lævothyroxine. Advantage of Liothyronine therapeutically lies in high potency and in promptness of action on "target cells".

*Dose.* 10-100 micrograms daily in divided doses.

## FORMULARY

### **\*Iodine**

Physical and chemical properties of the element *Iodine*, see BP.

**\*AQUEOUS IODINE SOLUTION** (Lugol's Solution).

Contains 5 per cent w/v of Iodine and 10 per cent w/v of Potassium Iodide in Purified Water.

*Dose.* 0.3-1 ml.

### **\*Methylthiouracil**

4-Hydroxy-2-mercapto-6-methylpyrimidine.

Bitter powder very slightly soluble in water.

*Dose.* Controlling, 0.2-0.6 G. daily.

Maintenance, 50-200 mg. daily.

**\*METHYLTHIOURACIL TABLETS**

A Tablet contains 50 mg.

### **\*Carbimazole**

2-Ethoxycarbonylthio-1-methylglyoxaline.

Bitter powder, almost insoluble in water.

*Dose.* Controlling, 30-60 mg. daily.

Maintenance, 5-20 mg. daily.

**\*CARBIMAZOLE TABLETS**

A Tablet contains 5 mg.

### **\*Potassium Perchlorate**

KClO<sub>4</sub>.

White crystalline powder soluble in 15 parts of water.

*Dose.* 600-1,200 mg.

\* These preparations are mentioned here in relation to the management of disorders of the thyroid gland.



## INSULIN AND ORAL HYPOGLYCÆMIC AGENTS

### **Insulin Injection**

#### *Soluble Insulin.*

A sterile solution of the protein hormone insulin, extracted from mammalian pancreas. A clear, colourless fluid. Contains 20, 40 or 80 Units per ml.

The *dose* of Soluble Insulin and of the other Insulins mentioned below is determined by the needs of the patient.

### **Protamine Zinc Insulin Injection**

A sterile suspension of insulin with a suitable protamine and zinc chloride.

Contains 40 or 80 Units per ml.

### **Globin Zinc Insulin Injection**

#### *Globin Insulin.*

A colourless, sterile solution of insulin with a suitable globin and zinc chloride.

Contains 40 or 80 Units per ml.

### **Insulin Zinc Suspension**

(Lente Insulin.)

A sterile buffered suspension of insulin with zinc chloride, consisting of 7 parts IZS (crystalline) and 3 parts IZS (amorphous). A turbid liquid.

Contains 40 or 80 Units per ml.

### **Insulin Zinc Suspension (Crystalline)**

(Ultralente Insulin.)

A sterile, buffered suspension of insulin with zinc chloride, the insulin being in the form of insoluble crystals. A turbid liquid.

Contains 40 or 80 Units per ml.

## FORMULARY

### **Insulin Zinc Suspension (Amorphous)**

(Semilente Insulin.)

A sterile, buffered suspension of insulin with zinc chloride, the insulin being in the form of insoluble amorphous particles. A turbid liquid.

Contains 40 or 80 Units per ml.

### **\*Tolbutamide**

("Rastinon.")

N-Butyl-N'-toluene-*p*-sulphonylurea.

White crystals, insoluble in water.

*Dose.* According to need of patient. Usually 1 G. thrice daily, decreasing to 0.5 G. twice or thrice daily.

### **\*Chlorpropamide**

("Diabenesc.")

1-(*p*-Chlorobenzenesulphonyl)-3-propylurea.

A white crystalline powder.

*Dose.* According to the needs of patient. Usually 100-500 mg. daily.

## **ADRENAL STEROIDS AND CORTICOTROPHIN**

### **Deoxycortone Acetate**

21-Acetoxy pregn-4-ene-3:20-dione.

Odourless, crystalline powder almost insoluble in water. Protect from light.

*Dose.* By intramuscular injection, 2-5 mg. daily.

Total implantation dose, 0.1-0.4 G.

#### **DEOXYCORTONE ACETATE IMPLANTS**

Sterile cylinders prepared by fusion or heavy compression of Deoxycortone Acetate without the addition of any other substance. Each is in sealed sterile container.

An implant contains 100 mg.

\* These drugs are not Insulins but are considered here as oral anti-diabetic drugs.

## DILLING'S CLINICAL PHARMACOLOGY

### DEOXYCORTONE ACETATE INJECTION

A sterile solution of Deoxycortone Acetate in Ethyl Oleate or other suitable ester or fixed oil.

*Dose.* 2-5 mg. daily by intramuscular injection.

1 ml. of solution contains 5 mg.

“PERCORTEN M CRYSTULES”—a suspension of microcrystalline deoxycortone trimethylacetate in aqueous isotonic buffered solution. 1 ml. contains 25 mg.

### Cortisone Acetate

21-Acetoxy-17 $\alpha$ -hydroxypregn-4-ene-3:11:20-trione.

Prepared from extracts of the cortex of the adrenal gland or by partial synthesis.

White crystalline powder, almost insoluble in water.

*Dose.* 50-300 mg. daily in divided doses.

For replacement therapy, 12.5 to 50 mg. daily.

By intramuscular injection, 50-200 mg. daily, in single or divided doses.

### CORTISONE ACETATE INJECTION

Sterile suspension of Cortisone Acetate in *very fine powder* in Sodium Chloride Injection.

1 ml. of suspension contains 25 mg.

### CORTISONE ACETATE TABLETS

The Tablet contains 25 mg.

### Hydrocortisone

11 $\beta$ :17 $\alpha$ :21-trihydroxypregn-4-ene-3:20-dione.

Prepared by partial synthesis. White crystalline powder insoluble in water. Soluble in 40 parts of alcohol (95 per cent).

*Dose.* In treatment of acute adrenocortical insufficiency, by intravenous infusion, 0.1 G.

## FORMULARY

### HYDROCORTISONE INJECTION

A sterile Alcoholic Hydrocortisone solution containing 100 mg. of Hydrocortisone in 20 ml. Mix immediately before use with 500 ml. of Dextrose Injection (5 per cent w/v) or Sodium Chloride Injection.

### HYDROCORTISONE OINTMENT

Contains 1 per cent of Hydrocortisone in ointment base.

### Hydrocortisone Acetate

21-acetoxy-11 $\beta$ :17 $\alpha$ -dihydroxypregn-4-ene-3:20-dione.

Prepared by partial synthesis. White crystalline powder insoluble in water; slightly soluble in alcohol.

*Dose.* By intra-articular injection, 5-50 mg.

### HYDROCORTISONE ACETATE INJECTION

A suspension of Hydrocortisone Acetate in Sodium Chloride Injection. Unsuitable for systemic use. Protect from light.

1 ml. contains 25 mg.

### HYDROCORTISONE ACETATE OINTMENT

Contains 1 per cent of Hydrocortisone Acetate in ointment base.

### HYDROCORTISONE ACETATE EYE-DROPS

A buffered isotonic suspension containing 1 per cent w/v of Hydrocortisone Acetate.

### HYDROCORTISONE ACETATE EYE OINTMENT

2.5 per cent of Hydrocortisone Acetate in a suitable Eye Ointment base.

### Hydrocortisone Sodium Succinate

Sodium 21-(3-carboxypropionyloxy)-11 $\beta$ :17 $\alpha$ -dihydroxypregn-4-ene-3:20-dione.

Readily *soluble* in water.

*Dose.* In treatment of acute adrenocortical insufficiency, by intravenous infusion 0.1 G. in 2 ml. water.

### **Fludrocortisone Acetate**

(9 $\alpha$ -Fluorohydrocortisone.)

White crystalline powder very slightly soluble in water.

*Dose.* 0.125-0.25 mg. (usually as a supplement to cortisone acetate). In acute deficiency 1 mg. once daily for 3 days.

### **Prednisone**

Deltacortisone. White crystalline powder, almost insoluble in water. Prepared by partial synthesis.

*Dose.* 10-50 mg. daily in divided doses.

#### **PREDNISONE ACETATE**

Almost insoluble in water.

#### **PREDNISONE TABLETS**

1 Tablet contains 5 mg. of Prednisone.

### **Prednisolone**

Deltahydrocortisone. White crystalline powder almost insoluble in water. Prepared by partial synthesis.

*Dose.* 10-50 mg. daily in divided doses.

#### **PREDNISOLONE TABLETS**

1 Tablet contains 5 mg. of Prednisolone.

### **Corticotrophin**

Adrenocorticotrophic Hormone, ACTH.

A sterile preparation of the hormone obtained from the anterior pituitary gland. Protein. Protect from light.

*Dose.* By subcutaneous or intramuscular injection, 10-25 Units every 6 hours.

The Unit is contained in 0.88 mg. of the Standard Preparation of dry Corticotrophin.

#### **CORTICOTROPHIN INJECTION**

Sterile solution of Corticotrophin in Water for Injection.

## FORMULARY

### LONG-ACTING CORTICOTROPHIN PREPARATIONS

#### **"Cortrophin-Zinc"**

Corticotrophin with zinc hydroxide in a fine aqueous suspension. 1 ml. contains 20 or 40 Units for subcutaneous or intramuscular use.

#### **"H.P. Acthar Gel"**

Corticotrophin in a fluid gelatin medium.

1 ml. contains 20 or 40 Units for subcutaneous or intramuscular use.

### PITUITARY GLAND (POSTERIOR LOBE)

#### **Vasopressin Injection**

Aqueous solution containing the pressor and antidiuretic principles of the posterior lobe of the pituitary body. Store at a temperature as low as possible, but above its freezing-point.

1 ml. contains 20 Units (pressor).

*Dose.* 0.25–0.75 ml. by subcutaneous or intramuscular injection.

#### **"PITRESSIN TANNATE"**

Vasopressin tannate in oily suspension.

1 ampoule contains 1 ml. (5 pressor units).

#### **POWDERED PITUITARY (POSTERIOR LOBE)**

Amorphous powder. Unit is specific activity (oxytocic, antidiuretic or pressor) corresponding to that yielded by 0.5 mg. of the standard preparation of pituitary (posterior lobe). Protect from air and moisture in cool place.

*Dose.* According to needs of patient (for diabetes insipidus). Usually 10 mg. as snuff thrice daily (expensive compared with parenteral injections).

## ŒSTROGENS AND PROGESTOGENS

### Œstradiol

Crystalline powder almost insoluble in water.

1 Tablet contains 1 mg.

*Dose.* 1-10 mg. orally.

### Œstrone

Colourless plate-like crystals. Obtained from urine of pregnant women and pregnant mares; it is also synthesised.

1 Tablet contains 1 mg.

*Dose.* 1-10 mg. orally.

### Œstriol

White crystalline powder obtained from pregnancy urine; almost insoluble in water.

*Dose.* Usual is 0.12 mg. up to 4 times daily.

### Œstradiol Monobenzoate

Prepared by the reduction of œstrone and benzylation of the  $\beta$ -œstradiol produced. Insoluble in water. Protect from light.

*Dose.* By intramuscular injection, 1-5 mg. daily.

#### ŒSTRADIOL MONOBENZOATE INJECTION

Solution of Œstradiol Monobenzoate in suitable oil.

1 ml. contains 1 mg.

*Dose.* 1-5 mg. intramuscularly daily.

### Ethinylœstradiol

This is semisynthetic, prepared from œstrone. White powder almost insoluble in water. Protect from light. The most potent œstrogenic substance in use.

*Dose.* Treatment of menopausal symptoms, 0.01-0.05 mg. daily.  
Suppression of lactation, 0.1 mg. thrice daily for 3 days, followed by 0.1 mg. daily for 6 days.

Treatment of carcinoma of prostate, 1-2 mg. daily.

## FORMULARY

### ETHINYLŒSTRADIOL TABLETS

1 Tablet contains 0.02 mg.

### Stilbœstrol

3:4-di-*p*-Hydroxyphenylhex-3-ene.

Synthetic crystalline powder very slightly soluble in water.

*Dose.* Menopausal symptoms, 0.1–1 mg. daily.

Suppression of lactation, 5 mg. thrice daily for 3 days,  
followed by 5 mg. daily for 6 days.

Carcinoma of prostate, 10–20 mg. daily.

### STILBŒSTROL TABLETS

1 Tablet contains 0.5 mg.

### STILBŒSTROL DIPROPIONATE

White crystalline powder. Soluble 1 in 45 of fixed oil.

*Dose.* Oral, 1–5 mg.

Intramuscular, 5–10 mg.

### Dienœstrol

A colourless crystalline powder.

*Dose.* Menopausal symptoms, 0.5–5 mg. daily.

Suppression of lactation, 15 mg. thrice daily for 3 days,  
followed by 15 mg. daily for 6 days.

Carcinoma of prostate, 15–30 mg. daily.

### DIENŒSTROL TABLETS

1 Tablet contains 1 mg.

### Hexœstrol

Colourless crystalline powder, almost insoluble in water.

*Dose.* 1–5 mg. daily.

### HEXŒSTROL TABLETS

1 Tablet contains 1 mg.

### Progesterone

Pregn-4-ene-3:20-dione.

Colourless crystals insoluble in water.

*Dose.* According to needs of patient.



## DILLING'S CLINICAL PHARMACOLOGY

### PROGESTERONE INJECTION

Solution of Progesterone in suitable oil.

1 ml. contains 10 mg.

### Ethisterone

17 $\beta$ -Hydroxypregn-4-en-20-yn-3-one.

White crystalline powder insoluble in water. Protect from light.

*Dose.* 25-100 mg. daily orally.

#### ETHISTERONE TABLETS

1 Tablet contains 25 mg.

## ANDROGENS

### Testosterone

17 $\beta$ -Hydroxyandrost-4-en-3-one.

Prepared from dehydro~~epi~~androsterone.

White crystalline powder almost insoluble in water. Protect from light.

*Dose.* Total implantation dose 0.1-0.6 G.

#### TESTOSTERONE IMPLANTS

Sterile cylinders of Testosterone without the addition of any other substance. Protect from light. 1 implant contains 100 mg.

### Testosterone Propionate

White crystalline powder. Protect from light.

*Dose.* By intramuscular injection, 5-25 mg. daily.

#### TESTOSTERONE PROPIONATE INJECTION

Solution of Testosterone Propionate in suitable oil. 1 ml. contains 10 mg.

*Dose.* By intramuscular injection, 5-25 mg. daily.

### Methyltestosterone

17 $\beta$ -Hydroxy-17 $\alpha$ -methylandrost-4-en-3-one.

White crystalline powder, almost insoluble in water. Slightly hygroscopic. Store in well-closed container. Protect from light.

*Dose.* 25-50 mg. orally daily for a man;

5-20 mg. orally daily for a woman.

## FORMULARY

### METHYLTESTOSTERONE TABLETS

1 Tablet contains 5 mg.

### Parathyroid Injection (USP)

Aqueous solution of the water-soluble principle or principles of the parathyroid glands, which have the property of relieving the symptoms of parathyroid tetany.

1 ml. contains not less than 100 USP parathyroid Units.

*Dose.* 25–100 Units intramuscularly.

#### “PARATHORMONE”

An aqueous solution of the active principles of the parathyroid.

1 ml. contains 100 USP Units. Available in 5 ml. vials.

*Dose.* Up to 100 Units intramuscularly (see text).

## DRUGS ACTING ON THE UTERUS

(see Chapter 13)

### Oxytocin Injection

A sterile solution containing the oxytocic principle of the posterior lobe of the pituitary (glands of oxen or other mammals or by synthesis): 10 Units in 1 ml.

*Dose.* 2–5 Units subcutaneously or intramuscularly.

### Ergometrine

Ergonovine. An alkaloid obtained from Ergot. Slightly soluble in water.

*Dose.* 0.5–1 mg. by mouth; 0.25–0.5 mg. intramuscularly;  
0.125–0.25 mg. intravenously.

### Ergometrine Maleate

The hydrogen maleate of ergometrine. “A white or faintly yellow, odourless, slightly hygroscopic, microcrystalline powder” (BPC). Soluble 1 in 36 water.

*Dose.* 0.5–1 mg. by mouth; 0.25–1 mg. intramuscularly;  
0.125–0.5 mg. intravenously.

## DILLING'S CLINICAL PHARMACOLOGY

### ERGOMETRINE MALEATE TABLETS

A Tablet contains 0.5 mg.

### ERGOMETRINE MALEATE INJECTION

1 ml. contains 0.5 mg.

METHYLERGOMETRINE MALEATE ("Methergin") is available as Tablets of 0.125 mg., as a Solution for oral use (0.25 mg. per ml.) and as an Injection (0.2 mg. per ml.).

The following preparations are included in this section though they are not used as uterine stimulants:—

### **Ergotamine Tartrate**

The tartrate of an alkaloid of Ergot. A white crystalline powder; sparingly soluble in water (tartaric acid needed to keep solution clear). Used for the symptomatic relief of migraine.

*Dose.* 1-2 mg. orally as a single dose;

0.25-0.5 mg. subcutaneously or intramuscularly.

### ERGOTAMINE TARTRATE TABLETS

Sugar coated; contain 1 mg. ergotamine tartrate.

### ERGOTAMINE TARTRATE INJECTION

1 ml. contains 0.5 mg. ergotamine tartrate.

### **Dihydroergotamine Methanesulphonate**

A modified preparation of ergotamine used in migraine. Minimal oxytocic action and increased sympatholytic effect.

*Dose.* 2-4 mg. by mouth;

0.25-1 mg. intramuscularly or intravenously.

## FORMULARY

### DRUGS ACTING ON THE ALIMENTARY SYSTEM

(see Chapter 14)

#### BITTERS AND DIGESTIVES

##### **Gentian**

The dried fermented rhizome of *Gentiana lutea*.

*Compound Gentian Infusion*: 15–30 ml. Contains bitter-orange peel and dried lemon peel. The *Concentrated Compound Gentian Infusion* is normally used.

*Dose*. 2–4 ml.

##### **Quassia**

The dried wood of Jamaica quassia.

*Concentrated Quassia Infusion*: 2–4 ml.

Quassia is not now official (BP 1958). When Bitters are used they should be prescribed alone, and the Concentrated Gentian Infusion meets all ordinary requirements. The fresh Infusion was formerly used as an anthelmintic enema in threadworm infestation.

##### **Dilute Hydrochloric Acid**

Contains 10 per cent w/w HCl.

*Dose*. 0.6–8 ml. given in lemon juice or lemon squash.

##### **Pepsin**

Obtained from gastric mucous membrane of animals.

An amorphous powder, capable of dissolving not less than 2,500 times its weight of coagulated egg albumen. Soluble in water; activity destroyed on boiling. Active only in an acid medium.

*Dose*. 0.3–1 G.

##### **Pancreatin**

Obtained from animal pancreas. A hygroscopic powder containing the enzymes trypsin, lipase and amylase.

*Dose*. 0.5–1 G.

Various enteric-coated capsules and granules are available.

### **Sodium Tauroglycocholate**

A yellowish powder, with an odour of bile.

*Dose.* 120–400 mg.

## **EMETICS AND ANTI-EMETICS**

### **Apomorphine Hydrochloride**

A colourless, crystalline powder, soluble in water. Turns green on deterioration.

*Dose.* 2–8 mg. injected parenterally: an emetic, acting centrally.

### **Anti-emetics**

See Antihistamine Drugs.

### **Antacids**

#### **Magnesium Trisilicate**

$2\text{MgO}_3\text{SiO}_2$ . An odourless, tasteless, white powder, insoluble in water.

*Dose.* 0.3–2 G.

#### **Heavy\* Magnesium Oxide**

$\text{MgO}$ . A white, odourless powder, almost insoluble in water. Protect from light.

*Dose.* 300–600 mg. as antacid.

2–4 G. as laxative.

#### **Heavy\* Magnesium Carbonate**

$3\text{MgCO}_3, \text{Mg}(\text{OH})_2, 4\text{H}_2\text{O}$ . A white, odourless, tasteless powder, almost insoluble in water.

*Dose.* 300–600 mg. as antacid.

2–4 G. as laxative.

\* The "Light" variety of these preparations differs from the "Heavy" only in regard to this physical property—which depends on the method of preparation. "Light" preparations consist of very fine particles and are suitable for dispersal in *fluid mixtures*. "Heavy" preparations consist of relatively coarse particles, and because of their smaller bulk are preferred in dispensing *powders*.

## FORMULARY

### **Magnesium Hydroxide**

$\text{Mg}(\text{OH})_2$ . A white, amorphous, tasteless powder, almost insoluble in water. Protect from moisture.

*Dose.* 0.6-4 G.

### **Magnesium Hydroxide Mixture**

(Cream of Magnesia)

*Dose.* 4-16 ml.

### **Aluminium Hydroxide Gel**

An aqueous suspension of hydrated oxide of aluminium, containing 3.5-4.4 per cent w/w of  $\text{Al}_2\text{O}_3$ ; the suspension is white and viscid.

*Dose.* 4-8 ml.

### **Aluminium Hydroxide Tablets**

A Tablet contains 300 mg. dried aluminium hydroxide gel.

### **Sodium Bicarbonate**

$\text{NaHCO}_3$ . A white powder with a saline taste, soluble in water. Incompatible with acids, many alkaloidal salts and aspirin.

*Dose.* 1-4 G.

### **Calcium Carbonate**

$\text{CaCO}_3$ . A white, tasteless, microcrystalline powder, almost insoluble in water.

*Dose.* 1-4 G.

### **Calcium Hydroxide**

$\text{Ca}(\text{OH})_2$ . A soft white powder with an alkaline taste, slightly soluble in water. Rarely given as an antacid. The solution is sometimes used in skin lotions and other preparations applied externally.

### **Calcium Gluconate**

(Sec text p. 411.)

A white tasteless powder slowly soluble in water.

*Dose.* 1-4 G.

## DILLING'S CLINICAL PHARMACOLOGY

### CALCIUM GLUCONATE INJECTION

Solution of Calcium Gluconate in Water for Injection. It is a supersaturated solution and if solid particles are present the injection must not be used.

20 ml. contain about 2 G. of Calcium Gluconate.

*Dose.* 10-20 ml. intramuscularly or intravenously.

### Calcium Lactate

White powder, readily soluble in *hot* water.

*Dose.* 1-4 G.

### CALCIUM LACTATE TABLETS

1 Tablet contains 0.3 G.

### Bismuth Carbonate

A basic salt of varying composition. Creamy-white powder, insoluble in water, opaque to X-rays. A very weak antacid; "protective" effect on gastric mucosa is of doubtful therapeutic significance.

*Dose.* 0.6-2 G.

## PURGATIVES

### Agar

Obtained from various species of algæ. Thin, greyish flakes; swells to a gelatinous mass in cold water. Store in dry place.

*Dose.* 4-16 G.

### Magnesium Sulphate

$\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ . Colourless crystals, with saline taste, soluble in water.

*Dose.* 2-16 G.

### Liquid Paraffin

A number of liquid hydrocarbons. A transparent, almost tasteless, oily liquid, insoluble in water.

*Dose.* 8-30 ml.

## FORMULARY

### LIQUID PARAFFIN EMULSION

*Dose.* 8–30 ml.

### LIQUID PARAFFIN AND MAGNESIUM HYDROXIDE EMULSION

*Dose.* 8–30 ml.

### Castor Oil

The fixed oil expressed from the seeds of *Ricinus communis*. A. pale yellow viscid oil with an acid after-taste, soluble in alcohol.

*Dose.* 4–16 ml.

### Phenolphthalein

A white powder, almost insoluble in water.

*Dose.* 60–300 mg.

### Aloes

The solid residue from evaporation of the fluid drained from cut leaves of *Aloe*.

*Dose.* 120–300 mg.

### Cascara Sagrada

The dried bark of *Rhamnus purshiana*. Has a nauseous bitter taste

#### CASCARA ELIXIR

*Dose.* 2–4 ml.

#### CASCARA DRY EXTRACT

*Dose.* 120–250 mg.

### Senna Fruit

(Senna Pod.)

The dried ripe fruits of *Cassia acutifolia* or *Cassia angustifolia*.

*Dose.* 0.6–2 G.

#### SENNA ELIXIR

*Dose.* 2–4 ml.

D.C.P.—24\*



## DILLING'S CLINICAL PHARMACOLOGY

### “SENOKOT”

A biologically standardised extract of senna fruit, usually prescribed as Granules ( $\frac{1}{2}$ –1 teaspoonful).

### Glycerin Suppository

Prepared from gelatin, glycerin and water.

## DEMULCENTS

### Acacia

Dried exudate from stem and branches of various species of *Acacia*. Soluble in water. Used as an emulsifying and suspending agent.

### Tragacanth

Dried gummy exudate from various species of *Astragalus*. Used as a suspending agent.

### Gelatin

Extracted with boiling water from animal tissues. Insoluble in cold water, soluble in hot water, forming a jelly on cooling. Used in preparation of pastilles, pessaries and suppositories.

## FLAVOURING AGENTS AND CARMINATIVES

### Liquorice

The dried root of various species of *Glycyrrhiza*. Used as flavouring agent and demulcent.

Dose. 1–4 G.

### LIQUORICE LIQUID EXTRACT

Dose. 2–4 ml.

## FORMULARY

**Cinnamon Oil**

**Clove Oil**

**Dill Oil**

**Lemon Oil**

**Orange Oil**

**Peppermint Oil**

These volatile or essential oils are used as flavouring agents and carminatives.

*Dose.* 0.06-0.2 ml.

## SWEETENING AGENTS

**Dextrose**

(Glucose.)

A white granular powder with a sweet taste, soluble in water. Protect from moisture.

### DEXTROSE INJECTION

A sterile solution in Water for Injection. 5, 10, 25 and 50 per cent strengths.

**Lactose**

(Milk Sugar.)

A sugar obtained from milk whey. A white, crystalline powder, with a sweet taste, soluble in water. Widely used pharmaceutically to give bulk to small doses of potent drugs when these are prescribed in powders.

**Sucrose**

(Cane Sugar.)

Colourless crystals, with a sweet taste, obtained from sugar cane or beet, soluble in water. Used as a sweetening agent and demulcent.

### SYRUP

(Simple Syrup) Sucrose 66.7 per cent in water.

### **Saccharin**

White powder, with an intensely sweet taste. Used as a sweetening agent, and as a substitute for sucrose.

## **ANTIBACTERIAL AGENTS**

(see Chapter 15)

### **PENICILLINS**

#### **Benzylpenicillin**

Penicillin G.

The sodium or potassium salt of benzylpenicillin produced by the growth of *Penicillium notatum*, related organisms or by any other means. A white, finely crystalline powder, very soluble in water.

#### **BENZYL-PENICILLIN INJECTION**

A sterile solution of Benzylpenicillin in Water for Injection. The usual strength of the Solution is 250,000 Units in 1 ml. To be used within 14 days of preparation if a buffering agent is present, and stored at a temperature not exceeding 4° C.

*Dose.* Determined by the physician in accordance with the needs of the patient. Usual dose in the treatment of sensitive infection 250,000 to 1,000,000 Units 2 to 4 times daily by intramuscular injection.

#### **BENZYL-PENICILLIN TABLETS**

The Tablet contains 200,000 Units (unless prescriber specifies some other strength).

Storage precautions—see BP.

*Dose.* Determined by the physician in accordance with the needs of the patient.

#### **Procaine Penicillin**

The monohydrate of the procaine salt of benzylpenicillin, containing not less than 975 Units of penicillin per mg. A white, crystalline powder soluble in 200 parts of water.

## FORMULARY

### PROCAINE PENICILLIN INJECTION

A sterile suspension of Procaine Penicillin in Water for Injection containing suitable dispersing agents and a buffering agent may be added. Protect from light and store in a cool place.

*Dose.* By intramuscular injection 500,000–1,000,000 Units daily. A suspension containing 300,000 Units in 1 ml. is usually dispensed.

### FORTIFIED PROCAINE PENICILLIN INJECTION

A sterile suspension of Procaine Penicillin in Water for Injection containing Benzylpenicillin in solution. Prepared by adding Water for Injection to a sealed vial containing a mixture of Procaine Penicillin and Benzylpenicillin together with dispersing agents; a suitable buffering agent may be added. Usual strength of the Injection: each ml. contains 300,000 Units of Procaine Penicillin and 100,000 Units of Benzylpenicillin.

*Dose.* Determined by the physician in accordance with the needs of the patient.

### Benzathine Penicillin

NN'-dibenzylethylenediamine di(benzylpenicillin) containing a variable amount of water of crystallisation. A white, tasteless powder, almost insoluble in water.

*Dose.* By intramuscular injection, as a sterile suspension, 300,000–1,000,000 Units. The usual strength of the suspension is 300,000 Units in 1 ml.

### BENZATHINE PENICILLIN TABLETS

Tablets containing 200,000 Units in each are supplied if the prescriber does not specify the quantity in each tablet.

*Dose.* 300,000–600,000 Units every 6 hours.

### Phenoxymethylpenicillin

Penicillin V.

An antimicrobial acid obtained from *Penicillium notatum* or related organisms, or by any other means. A white, finely crystalline powder, poorly soluble in water. It is given by mouth only.

## DILLING'S CLINICAL PHARMACOLOGY

### PHENOXYMETHYLPENICILLIN TABLETS

Usual strength 125 mg. in each tablet.

*Dose.* 125-250 mg. every 4 hours.

### OTHER PENICILLINS

Benethamine Penicillin and Penethamate Hydriodide are referred to in the text.

## STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

### Streptomycin Sulphate

The sulphate of the antimicrobial base produced by *Streptomyces griseus* or by any other means. A white solid freely soluble in water. Dispensed in a sealed, sterile container and stored in a cool place.

#### STREPTOMYCIN SULPHATE INJECTION

A sterile solution of Streptomycin Sulphate in Water for Injection. It remains stable for at least 1 year if stored at a temperature not exceeding 20° C. A solution containing the equivalent of 0.33 G. of streptomycin base in 1 ml. is usually employed.

*Dose.* By intramuscular injection, the equivalent of 0.5-1 G. of streptomycin base daily.

### Dihydrostreptomycin Sulphate

A white solid, very soluble in water. Dispensed in sealed, sterile containers. NOT to be used for *intrathecal injection*.

#### DIHYDROSTREPTOMYCIN SULPHATE INJECTION

A sterile solution of Dihydrostreptomycin Sulphate in Water for Injection. The usual strength is the equivalent of 0.25 G. of Dihydrostreptomycin base per ml. It should be used within one week of preparation if stored at room temperature, or within one month when stored at a temperature not exceeding 4° C.

*Dose.* By intramuscular injection, the equivalent of 0.5-1 G. of dihydrostreptomycin base daily.

## THE TETRACYCLINES

### Chlortetracycline Hydrochloride

The hydrochloride of an antimicrobial substance of known chemical constitution produced by the growth of *Streptomyces aureofaciens* or by any other means. Yellow crystals, soluble in 75 parts of water; taste bitter.

#### CHLORTETRACYCLINE CAPSULES

Capsules containing chlortetracycline hydrochloride mixed with a suitable inert diluent. They usually contain 0.25 G. of Chlortetracycline Hydrochloride in each.

*Dose.* For an adult 1-3 G. daily in divided doses; for a child, 10-30 mg. per Kg. of body weight daily in divided doses.

#### CHLORTETRACYCLINE INJECTION

A sterile solution of Chlortetracycline Hydrochloride in Water for Injection containing a suitable buffering agent. Prepared by dissolving the contents of a sealed container in the requisite amount of Water for Injection immediately before use. Administered by intravenous infusion in a concentration not exceeding 0.1 per cent w/v Chlortetracycline Hydrochloride in Sodium Chloride Injection.

*Dose.* By intravenous injection, 0.25-0.5 G.

### Oxytetracycline Dihydrate

The dihydrate of an antimicrobial substance produced by the growth of *Streptomyces rimosus* or by any other means. A tan-yellow, crystalline powder, slightly soluble in water and with a slightly bitter taste.

#### OXYTETRACYCLINE TABLETS

Sugar-coated tablets containing 0.25 G. of Oxytetracycline Dihydrate in each. They should be stored in a well-closed container.

*Dose.* For an adult, 1-3 G. daily in divided doses; for a child 10-30 mg. per Kg. of body weight daily in divided doses.

## Oxytetracycline Hydrochloride

A yellow, crystalline powder, with a bitter taste; hygroscopic and freely soluble in water.

### OXYTETRACYCLINE AND PROCAINE INJECTION

A sterile solution in Water for Injection of Oxytetracycline Hydrochloride and Procaine Hydrochloride. Prepared by dissolving the contents of a sealed container in Water for Injection. To be stored at a temperature not exceeding 4° C. and used within 5 days of its preparation. *For intramuscular injection only.*

*Dose.* By intramuscular injection, in a concentration not exceeding 5 percent w/v: for an adult, 0.2-0.4 G. daily; for a child, 5 mg. per Kg. of body weight daily.

### OXYTETRACYCLINE INJECTION

A sterile solution in Water for Injection of Oxytetracycline Hydrochloride containing a suitable buffering agent. To be used within 48 hours of its preparation. *For intravenous injection only.*

*Dose.* By intravenous infusion, in a concentration not exceeding 0.1 per cent w/v: for an adult, 1-2 G. daily; for a child, 10-20 mg. per Kg. of body weight daily.

## Tetracycline Hydrochloride

The hydrochloride of tetracycline, which may be obtained by the catalytic reduction of chlortetracycline or oxytetracycline. A yellow, crystalline powder with a bitter taste. Amphoteric.

### TETRACYCLINE CAPSULES

Capsules containing Tetracycline Hydrochloride mixed with a suitable diluent. Usually supplied with 0.25 G. in each.

### TETRACYCLINE TABLETS

Sugar-coated tablets usually containing 0.25 G. of Tetracycline Hydrochloride in each.

*Dose.* As Capsules or Tablets, for an adult, 1-3 G. daily in divided doses; for a child, 10-30 mg. per Kg. of body weight daily in divided doses.

## FORMULARY

### TETRACYCLINE AND PROCAINE INJECTION

A sterile solution of Tetracycline Hydrochloride and Procaine Hydrochloride in Water for Injection with suitable buffering and stabilising agents. Prepared by dissolving the contents of a sealed container in Water for Injection; to be used within 24 hours of its preparation; *for intramuscular injection only.*

*Dose.* By intramuscular injection, 0.2-0.4 G. daily, in divided doses.

### TETRACYCLINE INJECTION

A sterile solution of Tetracycline Hydrochloride in Water for Injection containing a suitable buffering agent. Prepared by dissolving the contents of a sealed container in Water for Injection; to be used within 24 hours of its preparation; *for intravenous injection only.*

*Dose.* By intravenous injection 0.25-0.5 G.

A variety of preparations containing tetracyclines are available for local application.

### ADDITIONAL PROPRIETARY PREPARATION FOR ORAL USE

Capsules each containing tetracycline equivalent to 250 mg. of the hydrochloride buffered with sodium metaphosphate 380 mg. are available commercially.

## Erythromycin

A basic antimicrobial substance produced by the growth of *Streptomyces erythreus*. A white, slightly hygroscopic powder with a bitter taste. Soluble 1 in 1,000 in water.

### ERYTHROMYCIN TABLETS

Enteric-coated tablets containing 100 mg. of erythromycin in each, unless otherwise specified. Tablets containing 200 and 250 mg. are available.

*Dose.* 1-2 G. daily in divided doses.

Proprietary preparations of Erythromycin Glucoheptonate and Erythromycin Lactobionate are available for parenteral use. The solutions for injection should be prepared according to the manufacturer's instructions.



## Chloramphenicol

An antimicrobial substance produced by the growth of *Streptomyces venezuelae*; now mainly prepared synthetically. A whitish, very bitter crystalline powder; soluble 1 in 400 of water.

### CHLORAMPHENICOL CAPSULES

Capsules containing 250 mg. in each are available.

*Dose.* For an adult, 1.5–3 G. daily in divided doses; for a child, 50 mg. per Kg. of body weight daily in divided doses.

Proprietary preparations of Chloramphenicol Cinnamate and Chloramphenicol Palmitate, which are tasteless compounds, are available as flavoured suspensions containing in each 4 ml. the equivalent of 125 mg. of Chloramphenicol.

Preparations for intramuscular and intravenous injection are also available.

For local application: Chloramphenicol Ear-drops BNF (5 w/v solution in propylene glycol); Chloramphenicol Eye Ointment BPC (1 per cent in Eye Ointment Basis). Other preparations for local use available commercially.

## OTHER ANTIBIOTICS

### Neomycin Sulphate

A mixture of the sulphates of Neomycin, an antibiotic produced by the growth of a strain of *Streptomyces fradiae*.

*Doses.* By intramuscular injection: 10–15 mg. per Kg. of body weight daily in divided doses.

By mouth: 1 G. every 4 hours.

Proprietary preparations for application to the skin, the eye, ear and mouth are also available.

### Novobiocin

An antibiotic produced by the growth of *Streptomyces spheroides* and *Streptomyces niveus*. A pale yellow powder, soluble in water; stable in the dry state.

Proprietary preparations of the calcium and sodium salts are available.

*Dose.* 1–2 G. daily in divided doses.

### **Bacitracin**

One or more of the antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* and *B. subtilis* var. *Tracy*. A pale buff powder; hygroscopic; taste bitter. Freely soluble in water and unstable in aqueous solution. Contains not less than 50 Units per mg. Proprietary compound preparations containing bacitracin with other antibiotics for local application are available.

### **Polymyxin B Sulphate**

The sulphate of an antimicrobial peptide produced by various strains of *Bacillus polymyxa* or by any other means. A creamy-white, hygroscopic powder, freely soluble in water. Contains not less than 6,000 Units per mg.

*Usual dose.* By intramuscular injection: for an adult, 250,000 Units every 4 hours; for a child, 10,000–20,000 Units per Kg. of body weight daily in divided doses.

Preparations for external application are also available.

### **Vancomycin and Ristocetin**

Preparations are available for intravenous use in severe resistant staphylococcal infections.

### **Viomycin Sulphate**

The sulphate of an antimicrobial polypeptide produced by certain strains of *Streptomyces puniceus*. A pale yellow, hygroscopic powder soluble in water.

*Dose.* By deep intramuscular injection, the equivalent of 1–2 G. of Viomycin base twice weekly.

### **Cycloserine**

An antibiotic produced by *Streptomyces orchidaceus* and *Streptomyces garyphalus*. Now manufactured synthetically. 4-Amino-isooxazolidin-3-one. Dispensed as Tablets or Capsules each containing 250 mg.

*Dose.* Up to 1 G. daily in divided doses.

### **Tyrothricin**

A mixture of antimicrobial polypeptides produced by *Bacillus brevis*. Contains Gramicidin and Tyrocidine. A very stable, insoluble, off-white powder. For external use only in an ointment or as a solution. Usual strength 0.5 per G. or ml.

### **Framycetin Sulphate**

The sulphate of an antimicrobial substance produced by a strain of *Streptomyces decaris*.

For local use only, in an Ointment containing 1.5 per cent.

### **Nystatin**

A fungistatic of fungicidal substance produced by *Streptomyces noursei*. A yellow, insoluble powder, stable at 4°C.

Proprietary preparations include Tablets containing 100,000 Units and 500,000 Units; an Ointment containing 100,000 Units per G.

### **Fumagillin**

See text.

## **CHEMOTHERAPY OF TUBERCULOSIS**

### **Sodium Aminosalicylate**

The sodium salt of 4-amino-2-hydroxybenzoic acid. A white, crystalline powder with a sweet saline taste; soluble in 2 parts of water.

#### **SODIUM AMINOSALICYLATE TABLETS**

Sugar-coated Tablets containing 0.5 G. each.

#### **SODIUM AMINOSALICYLATE CACHETS**

Contain 1.5 G. in each.

*Dose.* 10-20 G. daily in divided doses. For details see text.

## FORMULARY

### Isoniazid

Isonicotinohydrazide.

Colourless crystals or an almost white crystalline powder; taste, slightly sweet at first, then bitter; soluble in 8 parts of water.

#### ISONIAZID TABLETS

Contain 50 mg. in each Tablet, unless otherwise specified. 100 mg. tablets are available.

To be kept in well-closed containers, protected from light.

*Dose.* 0.1-0.3 G. daily in divided doses.

### Iproniazid

"Marsilid"— see text.

### Pyrazinamide

See text.

## CHEMOTHERAPY OF LEPROSY

### Dapsone

4:4'-Diaminodiphenylsulphone.

A white or creamy-white, crystalline powder; taste, slightly bitter. Almost insoluble in water.

#### DAPSONE TABLETS

Each Tablet contains 0.1 G.

*Dose.* Initial dose 25-50 mg. twice weekly, increasing by 50-100 mg. every month to a maximum of 0.2-0.4 G. twice weekly.

### Solapsone

A complex sulphone consisting chiefly of the hydrated tetrasodium salt of 4:4'-di-(3-phenyl-1:3-disulphopropylamino)diphenylsulphone. An almost white, amorphous powder, very soluble in water.

## DILLING'S CLINICAL PHARMACOLOGY

### STRONG SOLAPSONE INJECTION

Contains Solapsone 50 per cent w/v, with exsiccated sodium bicarbonate in Water for Injection.

*Dose.* 2-5 ml. twice weekly by intramuscular or subcutaneous injection.

### SOLAPSONE TABLETS

Each Tablet contains 0.5 G.

*Dose.* 1-3 G. daily.

### Thiacetazone

*p*-Acetamidobenzaldehyde thiosemicarbazone.

A white or pale yellow crystalline powder with a bitter taste; insoluble in water.

### THIACETAZONE TABLETS

Each Tablet contains 25 mg.

*Dose.* 10-25 mg. increasing gradually to 200 mg. daily.

### Chaulmoogra and Hydnocarpus Oils

These oils have been almost entirely superseded by the sulphones in the treatment of leprosy (see text).

## SULPHONAMIDES

Chemical nomenclature is given in the text; structural formulæ are shown on page 745.

*For Systemic Use*

**Sulphadiazine**

**Sulphamerazine**

**Sulphadimidine**

**Sulphafurazole**

**Sulphasomidine**

## FORMULARY

All are nearly white, odourless powders, poorly soluble in water. Sulphadimidine has a bitter taste; the others are almost tasteless. Dispensed as Tablets, 0.5 G. in each.

*Dose.* 3 G. initially; 1 to 1.5 G. every 4-6 hours subsequently. See text.

### **Sulphadimidine Sodium**

A white powder, soluble 1 in 2.5 of water; pH of solution about 10.5.

#### **SULPHADIMIDINE SODIUM INJECTION**

A sterile solution in Water for Injection; usual strength 1 G. in 3 ml.

*Dose.* By intravenous injection, 1-2 G.

### **Sulphafurazole Diethanolamine**

A derivative of sulphafurazole very soluble in water, available as "Gantrisin" in ampoules of 5 ml. Contains the equivalent of 400 mg. of sulphafurazole per ml.

*Dose.* By intravenous injection, 2 G.

### **Trisulphonamide Tablets**

Each contains sulphadiazine 185 mg., sulphamerazine 130 mg. and sulphathiazole 185 mg.

*Dose.* As for single sulphonamides.

## **SULPHONAMIDES FOR INTESTINAL CHEMOTHERAPY**

### **Phthalylsulphathiazole**

A white powder almost insoluble in water.

## DILLING'S CLINICAL PHARMACOLOGY

### PHTHALYLSULPHATHIAZOLE TABLETS

Each contains 0.5 G.

*Dose.* 10-15 G. daily in divided doses.

### Succinylsulphathiazole

A yellowish, white powder, soluble 1 in 5,000 in water.

### SUCCINYLSULPHATHIAZOLE TABLETS

Each contains 0.5 G.

*Dose.* 10-20 G. daily in divided doses.

### Sulphaguanidine

A white, crystalline powder, soluble 1 in 1,000 in water.

### SULPHAGUANIDINE TABLETS

Each contains 0.5 G.

*Dose.* 10-20 G. daily in divided doses.

### Salicylazosulphapyridine

A brownish-yellow powder almost insoluble in water.

Available as "Salazopyrin" in Tablets each containing 0.5 G.

*Dose.* 1 G. 4-6 times daily.

## SULPHONAMIDES FOR LOCAL USE IN THE EYE

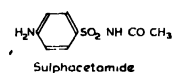
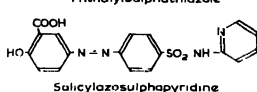
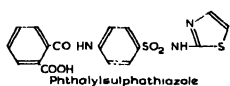
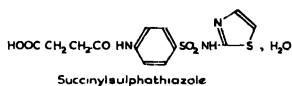
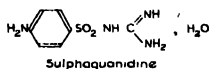
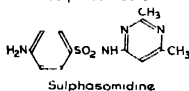
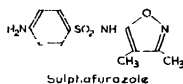
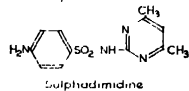
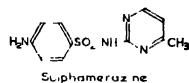
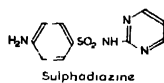
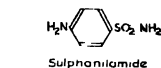
### Sulphacetamide Sodium

The sodium salt of sulphacetamide; white or yellowish-white crystals, soluble 1 in 1.5 of water. Used as Eye-drops containing 10-30 per w/v in a sterile aqueous solution buffered to pH 7.4 and as an Eye Ointment containing 6 per cent sulphacetamide sodium.

### Sulphafurazole Diethanolamine

Available as Eye-drops containing the equivalent of 4 per cent sulphafurazole and as an Eye Ointment of the same strength.

## FORMULARY



## ANTISEPTICS AND DISINFECTANTS

### Phenol

Carbolic acid. Faintly pink crystals, with characteristic odour. Caustic. Soluble in water.

#### LIQUEFIED PHENOL

Contains 80 per cent w/w in water. Various solutions of phenol, as antiseptic, 1-5 per cent.

### Cresol

A mixture of phenols and cresols obtained from coal-tar.

A yellowish liquid, darkening on exposure, soluble in water.

#### CRESOL AND SOAP SOLUTION

("Lysol.") A solution of cresol in a saponaceous solvent, containing about 50 per cent cresol.



## Thymol

A crystalline phenol, obtained from thyme oil. Colourless crystals, with pungent odour, almost insoluble in water.

*Dose.* 30–120 mg.

As an anthelmintic 1–2 G.

As mouth-wash about 0.05 per cent thymol is used.

## Chloroxylenol

4-Chloro-3:5-xyleneol.

White crystals, almost insoluble in water.

### CHLOROXYLENOL SOLUTION

Contains 5 per cent chloroxylenol. "Dettol Antiseptic" contains 4.8 per cent chloroxylenol.

## Chlorhexidine Diacetate

("Hibitane") Hexamethylenebis [N'-(N-*p*-chlorophenylamidino)-guanidine acetate].

Odourless, colourless crystals. Soluble in water.

As antiseptic, solution of 0.5 or 1 per cent.

## Hexachlorophane, USP

Di(3:5:6-trichloro-2-hydroxyphenyl)methane.

A crystalline powder, with faint phenolic odour. Insoluble in water; soluble with heating in vegetable oils.

As antiseptic incorporated in soaps and creams (0.25 to 2 per cent).

## Alcohol

(95 per cent.)

A mixture of ethyl alcohol (ethanol) and water, obtained by distillation of fermented saccharine liquids or by synthesis. Contains not less than 94.7 per cent v/v, and not more than 95.2 per cent v/v of ethanol. A colourless fluid, with spirituous odour and characteristic taste; miscible with water.

Various official dilute alcohols—as an antiseptic 70 per cent by weight is the critical concentration.

## FORMULARY

### Formaldehyde Solution

(Formalin.)

An aqueous solution of formaldehyde, containing about 36 per cent formaldehyde. A colourless liquid, with characteristic pungent odour, miscible with water.

### Boric Acid

$\text{H}_3\text{BO}_3$ .

White crystals or powder, soluble in water.

Various lotions, eye-drops, ear-drops, ointments—1–5 per cent.

### Borax

Sodium Borate.  $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ .

Colourless crystals, soluble in water.

Various lotions, eye-drops, nasal lotions and solutions.

### Iodine

For physical properties of Iodine *see* BP.

AQUEOUS IODINE SOLUTION (Lugol's Solution)

Contains iodine 5 per cent, potassium iodide 10 per cent in water.

WEAK IODINE SOLUTION (Iodine Tincture).

Contains iodine 2·5 per cent, potassium iodide 2·5 per cent and water 2·5 per cent, in alcohol.

Various other solutions, paints, ointments, etc.

### Chlorinated Lime

A dull white powder, with the odour of chlorine. Contains not less than 30 per cent w/w available chlorine. Decomposes in air and moisture.

For purification of drinking water, 1 oz. to 2,000 gals.

Also used to disinfect utensils and excreta.

CHLORINATED LIME SOLUTION WITH BORIC ACID

(Eusol.)

Contains chlorinated lime 1·25 per cent and boric acid 1·25 per cent in water.

### **Potassium Permanganate**

$\text{KMnO}_4$ .

Dark purple crystals, with a metallic lustre: slowly soluble in water.

As gargle or mouth-wash 1 in 5,000 solution (a pink colour).

As irrigation 1 in 10,000 solution (faint pink colour).

### **Hydrogen Peroxide Solution**

A colourless liquid containing 5–7 per cent  $\text{H}_2\text{O}_2$ .

This is known as the "20 volumes" solution as it liberates 20 times its volume of oxygen. Solutions up to 30 per cent ("100 volumes") are available.

As gargle, mouth-wash—used undiluted, or diluted with up to 8 parts of water.

### **Mercurochrome**

Disodium 2:7-dibromo-4-hydroxymercurifluorescein.

Greenish, iridescent crystals, soluble in water forming a red solution.

Solutions in water, or alcohol, up to 2 per cent are weakly antiseptic.

### **Thiomersal**

("Merthiolate.")

Sodium *o*-(ethylmercurithio)benzoate. A cream-coloured crystalline powder, soluble in water.

Tinctures (1 in 1,000), solutions (1 in 1,000) suitable for skin antiseptics. Creams, ophthalmic ointments, etc.

### **Cetrimide**

A mixture of dodecyl-, tetradecyl- and hexadecyl-trimethylammonium bromides. A white powder, soluble in water.

Used as 0.1–1 per cent solution in water or alcohol.

## FORMULARY

### **Proflavine Hemisulphate**

The neutral sulphate of 2:8-diaminoacridine.

A red crystalline powder, slightly soluble in water.

Proflavine Solution contains 0.1 per cent proflavine.

Also cream, ear-drops, pessaries.

### **Acriflavine**

### **Aminacrine**

} Similar preparations and uses.

### **Dibromopropamidine Isethionate**

1:3-Di(4-amidino-2-bromophenoxy)propane di-2-hydroxyethanesulphonate.

White crystals, soluble in water.

Creams and ointments contain 0.15 per cent.

### **Crystal Violet**

Greenish crystals, slightly soluble in water. Very soluble in alcohol.

As an antiseptic 0.5 per cent aqueous solution, or alcoholic solution.

### **Brilliant Green**

Small golden crystals. Soluble in water and alcohol.

As antiseptic 0.5-1 per cent solution.

## BIOLOGICAL AGENTS

### DIPHTHERIA

#### **Diphtheria Vaccine**

*Formol Toxoid (FT).*

*Alum Precipitated Toxoid (APT).*

*Purified Toxoid Aluminium Phosphate (PTAP).*

*Toxoid Antitoxin Floccules (TAF).*

Used in *active* immunisation against diphtheria. Relative merits of preparations, indications for use, doses and methods of administration are mentioned in text.

### **Diphtheria Antitoxin**

Obtained by immunising horses. The animals are bled and the serum (which contains the specific antibody) is then suitably prepared and biologically assayed in Units.

Indications for use, doses and methods of administration are mentioned in text.

## **TETANUS**

### **Tetanus Vaccine**

A simple solution of tetanus toxoid.

Active immunisation.

Indications and doses: *see* text.

### **Tetanus Antitoxin**

Method of preparation similar to that of Diphtheria Antitoxin.

Indications for use, doses and methods of administration are mentioned in text.

## **WHOOPING COUGH**

### **Pertussis Vaccine**

A sterile suspension of "Phase 1 *Bordetella pertussis* organisms having a potency of at least 1·5 times that of the standard preparation".

*Doses. See* text.

## **SCARLET FEVER**

### **Scarlet Fever Prophylactic**

A solution of the toxin of *Streptococcus hæmolyticus*.

It is used as an antigen in *active* immunisation against scarlet fever. The unit of dosage is a Skin Test Dose. *See* text.

### **Scarlet Fever Antitoxin**

Method of preparation similar to that of Diphtheria Antitoxin.

*Doses. See* text.

## FORMULARY

### GAS GANGRENE

#### Mixed Gas-gangrene Antitoxin

A polyvalent antitoxin.

Separate antitoxin fractions also available.

*Doses.* See text.

### TUBERCULOSIS

#### BCG Vaccine

Bacillus Calmette-Guérin is used. Standardised for its content of living organisms. Must be used within 10 days of preparation.

Indications for use and methods of administration are mentioned in text.

### TYPHOID

#### Typhoid Parathyroid A and B Vaccine

1 ml. contains *Salmonella typhi* 1,000 million, *S. paratyphi* A 500 or 750 million, and *S. paratyphi* B 500 or 750 million.

*Doses* and methods of administration—see text.

### POLIOMYELITIS

#### Poliomyelitis Vaccine

Contains three types of poliomyelitis virus grown on monkey kidney tissue culture and inactivated by means of formaldehyde.

*Dose.* 1 ml. intramuscularly followed by a further injection 3–6 weeks later, and a third dose after an interval of not less than 7 months.

See also use of Gamma Globulin (p. 535).

### YELLOW FEVER

#### Yellow Fever Vaccine

“An aqueous suspension of chick embryo containing living virus vaccine of yellow fever virus, strain 17D, which is virulent for mice but avirulent for man.”

For standardisation and dosage, see text.

## SMALLPOX

### Smallpox Vaccine

The preparation contains living vaccinia (cowpox) vaccine.

Obtained from lesions on the skin of healthy calves (calf lymph) or from membranes of inoculated chick embryos.

*Dose.* 0.02 ml. by scarification—*see* text.

### Mixed Vaccines

*Diphtheria-Tetanus Prophylactic.*

*Diphtheria-Tetanus and Pertussis Vaccine.*

*Diphtheria and Pertussis Vaccine.*

*Other Vaccines* include those given to protect against *Cholera*, *Plague*, *Rabies*, *Typhus* and *Staphylococcal* infections.

A brief account of these preparations is given in the text.

*Other Protective Sera* include those occasionally used in *Anthrax*, *Botulism*, *Dysentery* (Shiga), and *Leptospira* infections (*see* text).

### Human Gamma Globulin

Provides protective antibodies which may be used therapeutically in special circumstances to modify the course of infection due to *Measles*, *Rubella*, *Poliomyelitis* and *Infectious Hepatitis* (*see* text).

### Diagnostic Agents

Schick Test Toxin.

Schick Control.

Dick Test Toxin.

Dick Control.

Tuberculin Purified Protein Derivative.

The doses and uses of these diagnostic agents are discussed in the text. The technical procedures are described in books of reference, and skill in performing the tests is acquired only by practical instruction.

# DRUGS USED IN SYPHILIS, PROTOZOAL INFECTIONS AND METAZOAL INFESTATIONS

## ANTILUETIC DRUGS

(see Chapter 16)

**Penicillins**—Sec p. 732.

### Organic Arsenicals

*Neoarsphenamine*

*Sulpharsphenamine*

*Oxophenarsine Hydrochloride*

*Dichlorophenarsine*

} See text.

### Precipitated Bismuth

Finely divided metallic bismuth. A dull-grey powder, easily diffusable in water.

#### BISMUTH INJECTION

A sterile suspension of Precipitated Bismuth 20 per cent w/v with chlorocresol and dextrose in Water for Injection. Given intramuscularly.

*Dose.* 0.5–1 ml. (100–200 mg. bismuth metal).

Other aqueous preparations of Bismuth for intramuscular injection include Bismuth Oxychloride, Bismuth Sodium Tartrate (neutral compound), and Bismuth Sodium Thioglycollate; and there is an oily injection of Bismuth Salicylate (see BPC).

### Mercury

See text.

## ANTIMONY COMPOUNDS

### TERVALENT COMPOUNDS

#### Antimony Sodium Tartrate

Sodium Antimonyltartrate; the corresponding potassium salt (tartar emetic) is similar in its actions but more toxic and irritant.

*Dose.* 30–120 mg. intravenously (2 per cent aqueous solution). Unsuitable for intramuscular or subcutaneous injection (irritant).



## **Stibophen**

Pentasodium antimonybiscatechol-3:5-disulphonate. Fouadin.

Less toxic than Antimony Sodium Tartrate.

*Dose.* 100-300 mg. intravenously.

### **STIBOPHEN INJECTION**

*Dose.* 1.5-5 ml. intravenously (100-300 mg. stibophen).

## **QUINQUIVALENT COMPOUNDS**

### **Ethylstibamine**

"A complex mixture consisting of *p*-aminobenzenestibonic acid largely as a tetramer, *p*-acetamidobenzenestibonic acid largely as a dimer, antimonious acid, and diethylamine, in the approximate molecular ratio 1:2:1:3" (*The Extra Pharmacopœia*.)

*Dose.* 200-300 mg. by intramuscular or intravenous injection.

Other quinquivalent preparations include Sodium Stibogluconate, Stibamine Glucoside, Urea Stibamine, and Diethylcarbamazine Citrate.

## **ANTIMALARIAL DRUGS**

### **Quinine Bisulphate**

Colourless, odourless crystals; very bitter taste. Soluble 1 in 10 of water; 1 in 1 of boiling water.

*Dose.* 300-600 mg.

#### **QUININE BISULPHATE TABLETS**

Sugar-coated tablet contains 300 mg. quinine bisulphate.

### **Quinine Dihydrochloride**

White odourless powder; very bitter taste. Soluble 1 in 0.5 of water.

*Dose.* 300-600 mg. by mouth or intravenously.

## FORMULARY

### QUININE DIHYDROCHLORIDE INJECTION

Is available (300 mg. in 1 ml.); must be diluted 10 times and injected *slowly*.

Other preparations of quinine include:

Quinine Hydrochloride and Quinine Sulphate;

Quinine Ethyl Carbonate which is almost tasteless and has therefore been used as an antimalarial for children.

### Mepacrine Hydrochloride

("Atebrin.") Quinacrine Hydrochloride.

2-Chloro-5-(4-diethylamino-1-methylbutylamino)-7-methoxyacridine dihydrochloride dihydrate.

A bright yellow, odourless crystalline powder with a bitter taste. Soluble 1 in 40 water. Administered in tablets.

*Dose.* Prophylactic 100 mg. daily; therapeutic 200-500 mg. daily in divided doses.

#### MEPACRINE HYDROCHLORIDE TABLETS

A Tablet contains 100 mg.

### Mepacrine Methanesulphonate

A bright yellow, odourless crystalline powder. Soluble 1 in 3 water. Administered intramuscularly.

*Dose.* 100-300 mg. as 3 per cent solution made up immediately before injection. Also given *slowly* intravenously in emergency.

### Pamaquin

Plasmoquin.

8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline 2:2'-dihydroxy-1:1'-dinaphthylmethane-3:3'-dicarboxylate.

An orange-yellow, odourless powder with a bitter taste. Insoluble in water.

*Dose.* 10-20 mg. Tablets available contain 20 mg.

Obsolescent: primaquine phosphate is preferred (see below).

### **Primaquine Phosphate**

8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline di(di-hydrogen phosphate).

*Dose.* 10-30 mg. of primaquine base (17.5-53 mg. primaquine phosphate) daily for 14 days.

Tablets are available (BNF) which contain 7.5 mg. of base.

### **Proguanil Hydrochloride**

("Paludrine.")

N<sup>1</sup>-*p*-Chlorophenyl-N<sup>5</sup>-isopropylidiguanide hydrochloride.

A white, odourless, crystalline powder with a bitter taste; sparingly soluble in water.

*Dose.* 100-400 mg. daily.

Tablet contains 100 mg.

### **Pyrimethamine**

("Daraprim.")

2:4-Diamino-5-*p*-chlorophenyl-6-ethylpyrimidine.

A white, almost odourless, tasteless, crystalline powder; Almost insoluble in water.

*Dose.* 25 mg. weekly.

Tablets are available containing 25 mg.

### **Amodiaquine Hydrochloride**

("Camoquin.")

7-Chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline dihydrochloride dihydrate.

A yellow, odourless, crystalline powder with a bitter taste.

*Dose.* 200-600 mg. weekly.

Tablets are available (BNF) containing 200 mg.

### Chloroquine Phosphate

("Avloclor.")

7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline diphosphate.

A white powder with a bitter taste. Very soluble in water.

*Dose.* In malaria: suppressive, 500 mg. weekly; therapeutic, 1 G. on first day and then 500 mg. daily. In amœbiasis: 0.5-1 G. daily.

*Note.* 1.6 G. Chloroquine Phosphate is equivalent to 1 G. Chloroquine base.

#### CHLOROQUINE PHOSPHATE TABLETS

Contain 250 mg.

### Chloroquine Sulphate

("Nivaquine.")

A white crystalline powder with a bitter taste. Soluble 1 in 3 water.

*Dose.* In malaria: suppressive, 400 mg. weekly; therapeutic, 800 mg. on first day and then 400 mg. daily.

In amœbiasis: 400-800 mg. daily.

*Note.* 1.3 G. Chloroquine Sulphate is equivalent to 1 G. Chloroquine base.

*Parenteral Injections* may be given. Intravenously, as a 5 per cent solution (500 mg.) 6-hourly; total 1-1.5 G. Intramuscularly, 500 mg. 6-hourly; 1-1.5 G.

### Hydroxychloroquine Sulphate

7-Chloro-4-[4-(N-ethyl-N-2-hydroxyethylamino)-1-methylbutylamino]quinoline sulphate.

Actions and uses - as for Chloroquine.

*Dose.* In acute malaria 1.6 G. followed by three further doses of 400 mg. in the next 48 hours. This preparation can also be given intravenously and intramuscularly. For suppression of malaria 400 mg. weekly.

CHLOROQUINE (as the sulphate or the phosphate or as hydroxychloroquine sulphate) is also used in lupus erythematosus and in rheumatoid arthritis.

## DRUGS USED IN AMÆBIC DYSENTERY

### **Emetine Hydrochloride**

The hydrochloride of Emetine—an alkaloid of ipecacuanha.

A colourless, odourless, crystalline powder with a bitter taste. Soluble in water (1 in 8).

*Dose.* 30–60 mg. by intramuscular injection daily for 10 days (see text).

### **Emetine Bismuth Iodide (EBI)**

A complex iodide of emetine and bismuth. A reddish-orange, odourless powder with a bitter, acrid taste.

*Dose.* 60–200 mg. daily.

Available in Tablets (BNF) which are enteric-coated and contain 60 mg. EBI.

### **Bismuth Glycollylarsanilate**

("Milibis.")

Bismuthyl *p*-glycollamidophenylarsonate.

An odourless, yellowish-white to flesh-coloured powder; very slightly soluble in water.

*Dose.* 500 mg. by mouth thrice daily for 7 days: often given as supplement to chloroquine therapy in amæbic hepatitis. Tablets available containing 250 mg.

### **Carbarsone**

*p*-Ureidophenylarsonic acid.

A white powder, sparingly soluble in water.

*Dose.* 120–250 mg.

Available as Tablets containing 250 mg. given orally: 250 mg. twice daily for 10 days and repeated if necessary after 10 days.

*Enema.* 2 G. in 200 ml. 2 per cent warm sodium bicarbonate solution: given alternate evenings; not more than five enemata.

## FORMULARY

### Acetarsol

Acetarsonic. 3-Acetamido-4-hydroxyphenylarsonic acid.

A white, odourless, crystalline powder containing approx. 27 per cent of As.

*Dose.* 60–250 mg. (not more than 1 G. in 24 hours).

Used in chronic amœbiasis (Tablets containing 250 mg. twice or thrice daily for 10 days) usually in conjunction with emetine or chiniofon therapy.

### Iodochlorhydroxyquinoline

5-Chloro-8-hydroxy-7-iodoquinoline.

A brownish-yellow powder, almost insoluble in water.

*Dose.* 250 mg. thrice daily for 10 days. Not more than 1 G. in 24 hours. Course may be repeated after 10 days.

Various chlorohydroxyquinolines are available for staphylococcal skin infections ("Quinolol" Ointment).

### Di-iodohydroxyquinoline

("Diodoquin.")

8-Hydroxy-5:7-di-iodoquinoline.

*Dose.* 600 mg. thrice daily (as Tablets containing 300 mg.).

Supplements emetine therapy in intestinal amœbiasis.

### Chloroquine

See Antimalarial Drugs (p. 757).

The sulphate (400–800 mg. daily) or the phosphate (0.5–1 G. daily) may be used: valuable in hepatic amœbiasis, but useless in intestinal amœbiasis.

### Oxytetracycline

### Fumagillin

} Antibiotics which are occasionally  
used as amœbicides (see text).

### Sulphonamides

Sometimes used at onset of therapy to combat bacillary dysentery which may co-exist with intestinal amœbiasis.

## ANTHELMINTICS

*Doses and Methods of Administration* are mentioned in the text.

### THREADWORM INFESTATION

#### **Piperazine**

Diethylenediamine.

Three preparations available—the *hydrate*, the *adipate*, and the *citrate*.

#### **Hexylresorcinol**

4-*n*-Hexylresorcinol.

#### **Diphenan**

*p*-Benzylphenyl carbamate.

Not the anthelmintic of choice in threadworm infestation.

#### **Crystal Violet**

Medicinal Gentian Violet.

Hexamethylpararosaniline hydrochloride.

### TAPEWORM INFESTATION

#### **Mepacrine**

See antimalarials (p. 755).

Doses and administration as *anthelmintic*; see text.

#### **Male Fern**

The ethereal Extract of Male Fern is a thick greenish-black fluid with an unpleasant pungent taste and smell. Dispensed in gelatin capsules; less commonly in a flavoured emulsion. See text.

#### **Pelletierine Tannate**

Effective anthelmintic in tapeworm infestation but rarely used in Britain (toxicity).

## FORMULARY

### **Dichlorophen**

Di(5-chloro-2-hydroxyphenyl)methane.

Effective and safe in *T. saginata* infestation, but contra-indicated in *T. solium* infestation (see text).

### **Santonin**

A crystalline lactone.

Effective vermifuge in ascariasis, but hexylresorcinol is preferred because it is less toxic.

### **Oil of Chenopodium**

Effective in ascariasis and in ankylostomiasis but some danger of toxic effects, especially in debilitated patients.

## HOOKWORM INFESTATION

### **Tetrachloroethylene**

### **Carbon Tetrachloride**

### **Oil of Chenopodium**

### **Thymol**

## FILARIAL INFESTATION

### **Diethylcarbamazine Citrate**

## SCHISTOSOMAL INFESTATION

### **Lucanthone Hydrochloride**



## HEAVY METALS AND METALLOIDS

(see Chapter 17)

### Silver Nitrate

Colourless crystals; soluble; bitter metallic taste. Available as fused stick mounted in plastic holder for topical application to skin or mucosa. On tissues, forms white silver proteinate which darkens to brown or black sulphide of silver.

A valuable astringent for limited application (small ulcer), otherwise obsolete. N.B. Danger of argyria.

### Silver Protein

Non-corrosive: antiseptic action of silver ion prolonged because metal released slowly. Eye-drops 5 per cent: useful but rendered obsolescent by preference for sulphacetamide or antibiotics.

### Lead Acetate

White crystals, efflorescent, and freely soluble. Acetous odour and sweet astringent taste. Never administered orally or parenterally (poisonous).

Employed *externally* as a *Lead Subacetate Solution*. (Strong and Dilute preparations) in various ways—Lotion, Liniment, Glycerin, Ointment, and Suppository (rarely used).

### Mercury

The metal was formerly administered (for example as "Grey Powder") internally, and in ointments for inunction to produce systemic effects on absorption (syphilis), but these uses are obsolete.

AMMONIATED MERCURY OINTMENT contains 2.5 per cent Ammoniated Mercury. Useful in impetigo, and as application to peri-anal skin in threadworm infestation (see text).

MERCURIC OXIDE EYE OINTMENT contains 1 per cent Yellow Mercuric Oxide.

## FORMULARY

### RED MERCURIC IODIDE

A powerful local antiseptic resembling mercuric chloride (corrosive sublimate). Solubility increases in presence of potassium iodide ("Binioidide Solution"); 1 in 5,000 to 1 in 500 as an antiseptic externally, but sensitisation to mercury may occur.

MERCURIC CHLORIDE (Perchloride of Mercury, corrosive sublimate) and *Mercurous Chloride* (Subchloride of Mercury, Calomel) are both obsolescent drugs.

### PHENYLMERCURIC NITRATE AND PHENYLMERCURIC ACETATE

Bacteriostatic, fungicidal and spermicidal (contraceptive Gels and Paste).

On skin 1 in 1,500 solution; ointments 0.05 per cent; vaginal douche 1 in 30,000.

### Mersalyl Acid

A mixture of *O*-carboxymethylsalicyl-(3-hydroxy-mercuri-2-methoxypropyl)amide and its anhydrides. Mersalyl Injection contains about 10 per cent of mersalyl acid and 5 per cent theophylline. See text (Diuretics).

### Copper

Used as Copper Sulphate: acts as astringent or corrosive according to circumstances (see text); bacteriostatic and fungicidal. Should not be given as emetic (gastritis).

### Zinc

*Zinc Oxide* and *Calamine* (basic carbonate) are important preparations for local application to skin: dusting powders, ointments, pastes, lotions (see Chapter 19). *Zinc Chloride* is a soluble salt and hence a powerful corrosive; weak solution (0.5-1 per cent) may be used as astringent-antiseptic wash. *Zinc Sulphate* also soluble but milder as astringent-antiseptic; used in eye lotions and eye-drops (0.25 per cent).

**Aluminium**

Used as *Alum* either aluminium potassium sulphate (potash alum) or aluminium ammonium sulphate (ammonia alum). Astringent: as a mouth wash or as vaginal douche 1-4 per cent. Styptic: bleeding point (on skin) touched with crystal of alum.

See also *Aluminium Hydroxide* (Gastric Antacids).

*Kaolin* is purified native aluminium silicate: insoluble; mainly used as basis for *Kaolin Poultice*. Also an adsorbent and can be given internally, but is less effective than *Charcoal* (Active Carbon).

**Arsenic****Bismuth**

} See Formulary for antiluetic drugs (p. 753).

**DIMERCAPROL AND CHELATING AGENTS****Dimercaprol**

BAL; British Anti-Lewisite; 2:3-dimercaptopropan-1-ol.

A clear, colourless or slightly yellow liquid with smell of garlic; soluble in water. Antidote for poisoning by arsenicals (see text); also in acute mercurial poisoning (given *early*), and where poisoning is due to gold preparations. Lead poisoning better treated by Sodium Calciumedetate (see below).

*Dose.* 2-3 mg. per Kg. body weight intramuscularly every 4 hours according to needs of patient.

**Sodium Calciumedetate**

(See text: *lead poisoning*.)

The calcium chelate of the disodium salt of ethylenediamine-NNN'N'-tetra-acetic acid. Given intravenously by drip: not more than 500 mg. per 15 Kg. body weight per hour. Daily dose should not exceed 1 G. per 15 Kg. body weight, and weekly dose should not exceed 5 G. per 15 Kg. body weight. Courses of treatment last one week with intervals of one week; total duration 30 days.

Also of value in poisoning by plutonium, copper, nickel and iron, and as a local application (ointment) for chrome ulcers.

**CHEMOTHERAPEUTIC AGENTS IN  
MALIGNANT AND ALLIED DISEASES**

(see Chapter 18)

**Mustine Hydrochloride**

Chlorethazine Hydrochloride. Nitrogen Mustard.

Di(2-chloroethyl)methylamine hydrochloride.

A white hygroscopic powder, very soluble in water. Solutions rapidly lose their activity, and for therapeutic purposes are freshly prepared. Available in vials of 10 mg.

*Dose.* 0.1 mg./Kg. body weight daily. Maximum single dose 8 mg. Intravenous infusion (see text).

*N.B.* Mustine Hydrochloride is highly toxic: it is a strong vesicant and causes severe nasal irritation.

**Chlorambucil**

("Leukeran.")

$\gamma$ -[*p*-Di(2-chloroethyl)aminophenyl]butyric acid.

A derivative of nitrogen mustard. Available in Tablets for oral administration ("Leukeran" tablets contain 2 mg. and 5 mg.).

*Dose.* 0.2 mg./Kg. body weight daily for 3-6 weeks.

**Busulphan**

("Myleran.")

1:4-Di(methanesulphonyloxy)butane.

A white crystalline powder, sparingly soluble in water.

*Dose.* 4-6 mg. daily according to the hæmatological response.

Tablets of 0.5 and 2 mg. are available.

**Tretamine**

TEM; Triethanomelamine; Tri-ethylene Melamine.

2:4:6-Tri(ethylencimino)-s-triazine.

Action similar to that of nitrogen mustard.

Variable rate of absorption and cumulation make its clinical use unsatisfactory (see text).

### **Colchicine**

An alkaloid obtained from *Colchicum autumnale*.

*Dose.* 0.5–1 mg.

Toxicity limits therapeutic use as antimitotic agent.

### **Demecolcine**

An alkaloid of *Colchicum*: also antimitotic but less toxic than colchicine.

*Dose.* As antimitotic, 6–12 mg. daily.

Larger doses sometimes used, but toxic effects then produced (diarrhoea, rash, etc.). Tablets available (1 mg.) and a solution for intravenous injection (1 ml. contains 1 mg.).

### **Urethane**

Ethyl carbamate.

Colourless crystals, freely soluble in water; saline taste.

*Dose.* 1–2 G.

Administered as tablets or as proprietary elixirs.

In multiple myelomatosis 1 G. thrice daily.

### **Mercaptopurine**

6-Mercaptopurine

*Dose.* 2.5 mg./Kg. body weight daily.

Tablets available as "Puri-Nethol" containing 50 mg.

Produces remission in acute leukæmia; children respond better than adults, and lymphoblastic types more amenable than granulocytic and monocytic types.

### **Aminopterin**

N-4-Aminopteroyl-L(+) -glutamic acid.

*Dose.* 0.25–0.5 mg.

A folic acid antagonist: blocks the action of folic acid in nucleic acid metabolism and inhibits cellular development.

Given in acute leukæmia in children; *in adults* toxic effects prohibit its use.

### **Teropterin**

Pteroyltriglutamic acid.

*Dose.* 10–20 mg. intramuscularly.

A folic acid antagonist: effects similar to those of aminopterin, but relatively non-toxic.

Used as a palliative in cases of malignant disease (improvement in general health and well-being); supplements other forms of therapy.

### **Steroid Therapy**

### **Sex Hormones**

} See text.  
Preparations listed in Formulary Chap 12.

## **DRUGS ACTING LOCALLY**

(see Chapter 19)

Some of the physical and chemical properties of these substances are mentioned briefly in the text, but detailed information is available in the BP and BPC. The preparations include:

**Protectives and Lubricants:** Starch, Chalk, Zinc Oxide, Purified Talc, Liquid Paraffin and Pyroxylin.

**Demulcents:** Gelatin and Glycerin.

**Emollients and Ointment Bases:** Olive Oil, Soft Paraffin, Hard Paraffin, Lard, Wool Fat, Wool Alcohols, Cetostearyl Alcohol, Beeswax and Glycerin.

**Soaps and Detergents:** Curd Soap, Hard Soap, Soft Soap and synthetic anionic soapless detergents.

**Suppository Bases:** Oil of Theobroma and Gelatin.

**Depilatory Agents:** Barium Sulphide.

**Sclerosing Agents:** Ethanolamine, Morrhuc Acid, Quinine and Urethane Injection.

**Insecticides:** Dicophane, Gamma Benzene Hexachloride, Derris, Benzyl Benzoate, Sulphur, Dimethyl Phthalate, Dibutyl Phthalate.

## DIAGNOSTIC DYES AND RADIO-OPAQUE SUBSTANCES

(see Chapter 20)

### **Fluorescein Sodium**

The di-sodium salt of fluorescein. An orange-red powder soluble in water, the solution being strongly fluorescent.

#### FLUORESCEIN EYE-DROPS

Contain 2 per cent fluorescein sodium.

### **Congo Red**

A reddish-brown powder, soluble 1:30 of water.

*Dose.* 100-200 mg. intravenously. (In diagnosis of amyloid disease 0.25 ml. per Kg. body weight of a 1 per cent solution of Congo Red is injected.)

### **Azovan Blue**

(Evans Blue.)

A bluish hygroscopic powder, soluble in water.

*Dose.* 25 mg. intravenously. (In determining plasma volume 5 ml. of a 0.5 per cent solution is injected.)

### **Methylene Blue**

Tetramethylthionine chloride. A greenish, crystalline powder, soluble in water.

*Dose.* 60-300 mg.

### **Indigo Carmine**

A blue powder, only slightly soluble in water.

*Dose.* 50-100 mg. subcutaneously or intramuscularly.  
8-16 mg. intravenously.

### **Sulphobromophthalein Sodium**

("Bromsulphalein.")

*Dose.* 5 mg. per Kg. body weight.

## FORMULARY

### **Barium Sulphate**

$\text{BaSO}_4$ . A white, tasteless powder, insoluble in water.

Various suspensions up to 100 per cent w/v are used in radio-diagnosis.

### **Iodised Oil Injection**

A sterile preparation, made by the addition of hydriodic acid to poppy-seed oil. A clear, oily liquid, insoluble in water.

*Dose.* As required for the diagnostic procedure.

### **Propyliodone**

N-Propyl 3:5-di-iodo-4-pyridone-N-acetate.

A white crystalline powder, almost insoluble in water.

#### PROPYLIODONE INJECTION

A sterile suspension of propyliodone 50 per cent w/v in Water for Injection.

*Dose.* As required for the diagnostic procedure.

#### PROPYLIODONE OILY INJECTION

A sterile suspension of propyliodone 60 per cent w/v in arachis oil.

*Dose.* As required for the diagnostic procedure.

### **Diodone Injection**

A sterile aqueous solution of the diethanolamine salt of 3:5-di-iodo-4-pyridone-N-acetic acid. A clear, straw-coloured liquid, available in 35, 50 and 70 per cent strengths.

*Dose.* The strength and volume required for the diagnostic procedure.

### **Iodoxyl**

The disodium salt of 3:5-di-iodo-N-methyl-4-pyridone-2:6-dicarboxylic acid.

White powder soluble in water.



## DILLING'S CLINICAL PHARMACOLOGY

### IODOXYL INJECTION

A sterile solution of Iodoxyl in Water for Injection.

A colourless liquid. Contains 75 per cent w/v of Iodoxyl.

*Dose.* (adult) 20 ml.

### Pheniodol

$\beta$ -(4-Hydroxy-3:5-di-iodophenyl)- $\alpha$ -phenylpropionic acid.

A creamy-white powder.

*Dose.* 3-6 G. as single dose.

### Iopanoic Acid

$\alpha$ -(3-Amino-2:4:6-tri-iodobenzyl)butyric acid.

A white powder, insoluble in water.

Iopanoic acid Tablet contains 0.5 G.

*Dose.* 2-6 G. as a single dose 10-15 hours before radiography.

### Iodipamide Methylglucamine NNR

("Biligradin.")

A crystalline powder, soluble in water.

*Dose.* 6 G. (20 ml. of 30 per cent solution) intravenously.

## RADIO-ACTIVE ISOTOPES

(see Chapter 21)

### Iodine-131

<sup>131</sup>I. Administered as a solution or injection of sodium radioiodide. Also used to "tag" human proteins.

Half-life 8 days.

#### SODIUM RADIO-IODIDE (<sup>131</sup>I) SOLUTION

A clear, colourless solution. Containers should be screened.

*Dose.* As determined by the physician.

### Phosphorus-32

<sup>32</sup>P. Administered as a solution or injection of sodium radio-phosphate. Half-life 14.3 days.

## FORMULARY

### SODIUM RADIO-PHOSPHATE ( $^{32}\text{P}$ ) SOLUTION

A clear, colourless solution. Containers should be screened.

*Dose.* As determined by the physician.

### Gold-198

$^{198}\text{Au}$ . Administered as a colloidal suspension stabilised with gelatin.

### Chromium-51

$^{51}\text{Cr}$ . Administered as sodium radio-chromate solution.

### Cobalt-60

$^{60}\text{Co}$ . Used in radiotherapy, and also as  $^{60}\text{Co}$ -labelled cyanocobalamin.

# APPENDIX III

## PRACTICAL PHARMACOLOGY AND PHARMACY—A LABORATORY COURSE FOR MEDICAL STUDENTS

*The work of each meeting of the Class is set out below. Full and accurate records of results should be made in a bound notebook. It is particularly important that "failures" or unusual effects should be mentioned and briefly discussed. The programme for each meeting should be read over carefully before-hand, otherwise the experiments are not likely to be completed in the time available.*

### FIRST MEETING

#### PRACTICAL PHARMACOLOGY

##### EXCRETION OF DRUGS IN THE URINE

Certain drugs are excreted in the urine, either unchanged or modified in various ways. The presence of these substances may lead to fallacious results when the urine is tested for sugar, ketones or urobilinogen.

*Benedict's Test.* To 5 ml. of Benedict's solution in a test-tube add 10 drops of urine and boil for 2 minutes. The presence of a reducing substance, for example glucose, is indicated by the appearance of a green, yellow or orange precipitate.

EXPERIMENT 1. Perform Benedict's Test on the urines provided which have been obtained as follows:

- (a) From a patient with diabetes mellitus.
- (b) Ordinary table sugar added to normal urine.

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- (c) From a patient having sodium salicylate 2 G. 4-hourly.\*
- (d) Sodium salicylate added to normal urine.

Make notes in each case under the following headings:

- (1) Record the result of the test.
- (2) Interpret this result within the limits of the experiment.
- (3) Explain the phenomena observed.

*Gerhardt's Test.* To 5 ml. urine in a test-tube add drop by drop a 10 per cent solution of ferric chloride. A dark reddish colour of varying intensity indicates the presence of aceto-acetic acid. If the urine is thoroughly boiled after it has been rendered distinctly acid with acetic acid, aceto-acetic acid is converted into acetone which is driven off, and no reaction is given.

EXPERIMENT 2. Perform Gerhardt's test on the urines provided. If a colour change occurs, repeat the test after acidifying and boiling the urine.

- (e) Urine from a patient in diabetic ketosis.
- (f) From a patient having sodium salicylate 2 G. 4-hourly.
- (g) Patient has had 1 G. of aspirin.
- (h) Aspirin has been added to normal urine.

Make notes in each case as above.

\* *Metric System.* The medical student is already familiar with weights and measures expressed in the Metric System. In the *British Pharmacopæia*, 1958, the doses of drugs are usually stated in the Imperial System as well as in the Metric System, but it is highly probable that in future editions of the BP only the Metric System will be used. It is therefore desirable that medical students should use the Metric System exclusively. The abbreviations used in this book (mg., G., ml., l.) are those officially recommended. On p. 785 tables of weights and measures in the Imperial System are set out for reference. Practitioners and students who prescribe only in the Metric System should nevertheless be able to convert quantities from one system to the other. A table of approximate equivalents is therefore included and it should be committed to memory. In this Appendix many of the doses are stated in both Metric and Imperial Systems: the student should note these examples of approximate equivalents.

**Ehrlich's Aldehyde Test.** To 5 ml. of urine add 1 ml. (10 drops) of Ehrlich's aldehyde reagent (0.25 per cent solution in normal hydrochloric acid of paradimethyl aminobenzaldehyde). A distinct pink or red colour develops in the cold if excess of urobilinogen is present.

EXPERIMENT 3. Perform this test on the urines provided:

(k) A patient with hepatitis.

(l) A patient receiving sulphadimidine 1 G. 4-hourly.

Make notes in each case as above.

### DRUGS ACTING ON THE SKIN

**Counter-irritants** are drugs applied to the skin which produce a local irritant action. They afford temporary relief of deep-seated pain. Examples are mustard, cantharidin, capsicin, turpentine.

EXPERIMENT 4. EFFECT OF A MUSTARD PLASTER. Apply a mustard plaster which has been soaked in warm water to the front of the forearm; cover with wet lint and fix with adhesive tape. Remove after 15 minutes, then examine the site for:

(a) Change in colour.

(b) Subjective sensation.

(c) Appreciation of light touch and pin-prick.

Record these observations at 5-minute intervals for 20 minutes and tabulate the results. What is the total duration of the rubefacient action of the plaster? Why is it necessary to moisten the plaster before applying it? Would you ever use a mustard plaster in general practice? Give your reasons.

**KAOLIN POULTICE.** Kaolin poultice consists of heavy kaolin (aluminium silicate), together with boric acid, thymol, methyl salicylate, oil of peppermint and glycerin. To prepare a kaolin poultice, warm the tin in a saucepan of hot water, spread the warm poultice on several layers of gauze or cotton wool, cover the surface with a separate double layer of gauze and bandage over the affected part. The temperature of the poultice should be carefully tested to avoid burning the skin.

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**EXPERIMENT 5.** Prepare a kaolin poultice and apply it to the skin of the back of the hand, leaving in place for at least 30 minutes. Describe the sensations you experience. How long does the poultice "retain its heat"? For what types of case would you consider using a kaolin poultice? Do you think it is a good form of treatment?

Frictional rubbing of the skin produces of itself certain alterations in vascularity and sensation. Menthol possesses peculiar properties of its own.

**EXPERIMENT 6.** (a) Rub an area of the right temple for 1 minute with a stick of hard paraffin.

(b) Rub a similar area of the left temple with a stick of menthol for the same time.

(CAUTION: Menthol may make your eyes smart.)

Describe the series of changes you note at 1-minute intervals over a period of 5 minutes in respect of:

- (i) Skin colour.
- (ii) Sensation.
- (iii) Appreciation of light touch, pain and hot and cold.

What is your explanation of these results?

**EXPERIMENT 7.** Add one crystal of menthol to a jug of hot water and inhale the steam. Describe the sensations you experience. Why are menthol inhalations used in treating upper respiratory affections?

**DEMONSTRATION. STERILISATION OF SYRINGES.** For the next two meetings of the class you will require to bring a sterile 2 ml. record syringe and needles in a sterile container. A method of sterilising the syringe will be demonstrated, and this will be found useful in general practice. Students should read the M.R.C. Memorandum, "The Care and Sterilisation of Syringes".

*Materials required:* 2 ml. Record syringe, preferably all-glass.  
3 hypodermic needles, No. 16 or 18.  
1 pair blunt dissecting forceps.  
Spirit-proof syringe case.

*Preparation of the Syringe.* Wash the syringe and needles in warm soapy water, rinse in plain water and dry. Smear a small quantity of liquid paraffin on the tip of the plunger, run it up and down the barrel a few times to lubricate it, and remove any excess of paraffin.

*To Sterilise the Syringe.* Wrap parts *separately* in gauze or lint and immerse in warm (but not hot) water in a clean saucepan with a lid. Stand the forceps up in the pan also. Bring the water to the boil and allow to boil for 5 minutes. Allow the forceps handle to cool, then use the forceps to transfer the syringe to the syringe case, which should be filled with a 70 per cent w/v solution of ethyl alcohol. This is the optimum strength for antiseptic action.

### PRESCRIPTIONS

During the first week of the Course the following exercises in prescription writing are to be written by each student. The principles of prescribing are discussed on pp. 5-7. You will have an opportunity to dispense a *selection* of the preparations which you have prescribed (p. 797).

- (1) A *lotion* for the relief of sunburn.
- (2) A *liniment* to be used for "fibrositis".
- (3) An antacid *powder* for the treatment of duodenal ulcer.
- (4) Antipyretic powders for a child aged 8 years with influenza.
- (5) A cough *mixture* for use in bronchitis.
- (6) A prescription for a patient aged 50 years with severe pain resulting from inoperable carcinoma.

## SECOND MEETING

### USE OF THE SYRINGE

Rinse your syringe and needles in boiled water to remove all trace of spirit. Each needle should be used only once, and should be resterilized by immersion in boiling water for 1 minute, or by holding in a flame for 10 seconds. Wash your hands before using the syringe, and avoid touching the plunger of the syringe

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or the shaft of the needle. If you lay the syringe down between injections, make sure that the needle does not touch the bench or anything else.

**PREPARATIONS FOR INJECTION.** Materials for injection are prepared in four ways:

1. *In Single-dose Ampoules.* These contain the drug for injection usually dissolved in 1 ml. of sterile water. This is opened immediately before use with a file in the manner demonstrated, and the contents drawn into the syringe.

*Examples.* Injection of carbachol 0.25 mg. in 1 ml.

Injection of nicotinamide 50 mg. in 1 ml.

2. *In Multiple-dose Vials.* The sterile solution of the drug is in a rubber-capped vial containing 5–30 ml.

*Examples.* Injection of soluble insulin, 5 ml. vials.

Injection of adrenaline hydrochloride 1 in 1,000,  
30 ml. vials.

Clean the rubber diaphragm with 70 per cent spirit.

Hold the vial inverted in the left hand.

Withdraw the plunger of the syringe to an amount equal to the volume to be injected, e.g. 1 ml. and push the needle through the cap. Inject air into the vial and withdraw the required amount of solution. Expel bubbles and adjust the volume of solution in the syringe accurately *before* removing the needle. Inject the material using the same needle.

3. Some substances for injection, e.g. certain preparations of penicillin, are provided in the form of a *dry powder contained in a rubber-capped vial*, to which sterile water must be added to make a solution immediately before use.

4. Certain drugs are sometimes dispensed in the form of *hypodermic tablets* which must be dissolved in sterile water immediately before use.

*Examples.* Injection tablet of morphine sulphate 15 mg.

Injection tablet of pilocarpine nitrate 10 mg.



The following method is employed in domestic use:

Half fill a teaspoon with tap water and bring to the boil over a small flame. Measure 1 ml. of this into a sterile syringe and discard the remainder. Place the hypodermic tablet in the spoon and dissolve by adding the water from the syringe. If the tablet contains a quantity of the drug other than what you wish to inject, calculate the correct amount as follows:

*Example.* Inject 10 mg. of morphine, using the 15 mg. tablet supplied.

Dissolve the tablet in 1.5 ml. of water; 1 ml. of this solution contains 10 mg. of morphine.

*Intradermal Injection.* The technique will be demonstrated. Remember the following points:

- (i) Avoid the neighbourhood of veins.
- (ii) Keep the skin well tensed.
- (iii) Keep the bevel of the needle up.
- (iv) Inject *across* the forearm rather than along it.
- (v) Keep the needle parallel with the skin.
- (vi) Success is indicated by the appearance of a definite bleb.

#### ACTION OF LOCAL ANÆSTHETICS ON SKIN AND MUCOUS MEMBRANES

EXPERIMENT 8. ACTION OF PROCAINE ON THE SKIN. Each student should inject into his or her partner and receive in return the following intracutaneous injections. Injections should be made at least 5 cm. apart, two on each forearm.

- (a) 0.1 ml. normal saline.
- (b) 0.1 ml. procaine hydrochloride 0.1 per cent.
- (c) 0.1 ml. procaine hydrochloride 0.1 per cent containing also adrenaline hydrochloride 0.01 per cent.
- (d) 0.1 ml. adrenaline hydrochloride 0.01 per cent.

Record the following observations on all four skin areas every 2 minutes for 20 minutes, and tabulate your results:

- (i) Subjective sensation.
- (ii) Appearance.

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- (iii) Analgesia to pin-prick (none, slight, moderate or complete analgesia or hyperalgesia).

Interpret these results.

### EXPERIMENT 9. ACTION OF ETHYL CHLORIDE ON THE SKIN.

Direct the spray of ethyl chloride on to a small area of skin on the back of the hand from a distance of 1 foot until there is frosting. Avoid inhalation of ethyl chloride vapour. Record the following at intervals of 1 minute for 5 minutes after commencing the spray:

- (i) Colour of skin.
- (ii) Subjective sensation.
- (iii) Appreciation of pain (pin-prick).

Tabulate your results.

What is the mode of action of ethyl chloride in this experiment?

What are the effects of inhaling ethyl chloride vapour?

What do you think are the advantages and disadvantages of ethyl chloride spray as a local anæsthetic agent? Would *you* use it for incising a septic finger?

**EXPERIMENT 10. ACTION OF PHENOL AND PROCAINE ON MUCOUS MEMBRANES.** Hold a small piece of cotton wool soaked in 2 per cent phenol solution to one-half of the lower lip for 2 minutes, and a similar piece soaked in 2 per cent procaine solution to the other half for the same period.

Describe the changes in appearance, subjective and objective sensation in each half of the lip, and note the duration of such changes.

Interpret your results. In what ways does the action of phenol when applied to the mucous membrane of the lip differ from the actions of procaine?

## ACTION OF DRUGS ON THE EYE

**DEMONSTRATION.** The correct method of instilling drugs into the eyes will be demonstrated.

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**EXPERIMENT 11.** Note the size of your partner's pupils, their reaction to light and on accommodation, and the distance of the near point of each eye (in cm.). One student instils into one conjunctival sac of his partner, two drops of 1 per cent cocaine hydrochloride solution. He in turn has two drops of  $\frac{1}{2}$  per cent homatropine sulphate solution placed in one conjunctival sac. The following observations are to be made and recorded at 5-minute intervals for 30 minutes for both drugs:

- (i) Size of pupil.
- (ii) Reaction to light.
- (iii) Reaction on accommodation.
- (iv) Distance of near point.
- (v) Vascularity of conjunctiva.
- (vi) Secretion of tears.
- (vii) Subjective sensations.

After 30 minutes add 1 drop of  $\frac{1}{4}$  per cent physostigmine solution to the eye being tested. Continue the observations as above for a further period of 30 minutes.

Tabulate the results for all four experiments. Explain your findings with reference to the mode of action of the drugs.

What is the explanation of the headache sometimes produced by physostigmine?

 (CAUTION: Do not attempt to drive a vehicle for a period of 12 hours after these drugs have been used.)

## WEEKEND WORK - PURGATIVES

Each member of the class will be provided with one of the following purgatives:

Aloes pills	(2) (0.5 G.)
Compound rhubarb pills	(2) (0.5 G.)
Cascara sagrada tablets	(2) (0.25 G.)
Phenolphthalein tablets	(2) (0.25 G.)
Compound effervescent powder (Seidlitz powder).	

The Powder should be taken first thing in the morning, on an empty stomach, in a tumbler of warm water. The other purga-

tives should be taken at night. Write a description of your experiences with the purgative noting the following points:

- (i) Time before evacuation occurs.
- (ii) Consistence and colour of stool.
- (iii) Gripping.
- (iv) Upset in the normal bowel rhythm.
- (v) Any other effects.

Describe the mode of action of the purgative you received.

### ***THIRD MEETING***

EXPERIMENT 12. EFFECTS OF PILOCARPINE. Using the 10 mg. hypodermic tablet of pilocarpine nitrate provided, prepare an injection of 6 mg. pilocarpine nitrate, and administer this subcutaneously to one another. Record the effects, at 5-minute intervals for 45 minutes, noting especially the following:

- (i) Perspiration.
- (ii) Salivation.
- (iii) Tear secretion.
- (iv) Flushing.
- (v) Other effects.

Describe the mode of action of pilocarpine. Why does it produce sweating?

What other drugs do you think might promote perspiration?

Note that pilocarpine has limited uses in therapeutics.

### **ACTION OF NITRITES**

In all experiments involving serial readings of blood pressure and pulse rate it is advisable first of all to make repeated control observations until a constant basal reading is obtained.

EXPERIMENT 13. Work in pairs. Obtain basal readings for pulse rate, respiration rate and blood pressure on one another. One subject then chews a tablet of glyceryl trinitrate 0.5 mg. and holds the fragments under his tongue. His partner makes and

## DILLING'S CLINICAL PHARMACOLOGY

tabulates observations every 2 minutes for 45 minutes of the following points:

- Pulse rate
- Respiration rate
- Blood pressure
- Subjective sensations
- Vasodilatation
- Other effects.

*Amyl Nitrite.* This drug is dispensed in the form of a vitrella, a small crushable glass capsule containing 0.2 ml. of the liquid, and enclosed in an absorptive and protective fabric. When required the capsule, wrapped in a handkerchief, is crushed between the finger and thumb and the vapour is inhaled.

EXPERIMENT 14. Sit down. Crush a capsule of amyl nitrite and inhale the vapour. Describe carefully the subjective effects you experience. Write a note comparing and contrasting the pharmacological action and therapeutic usefulness of glyceryl trinitrate and amyl nitrite. Which drug would you prescribe for patients with angina of effort, and why?

## FOURTH MEETING

### ACTION OF HISTAMINE ON THE SKIN

EXPERIMENT 15. Each student should inject intradermally into the skin of his partner's forearm 0.1 ml. of a 1 in 10,000 solution of histamine acid phosphate. Avoid the neighbourhood of veins. Observe carefully the effects of the injection, and record the following observations in your notebook every 2 minutes for 10 minutes, and then every 5 minutes until half an hour after the injection, or until the reaction has subsided:

Pain—character and intensity.

Pruritus.

Erythema—measure the exact area affected.

Wealing—measure the area and assess the degree.

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Make a drawing of the reaction as it appeared at its height.

Fifteen minutes after the injection apply the cream supplied to the skin and describe what change, if any, you notice. Explain the effects of histamine on blood vessels as demonstrated by this experiment.

### GARGLES AND MOUTH-WASHES

Gargles and mouth-washes usually consist of a dilute solution of a mild antiseptic agent. They are often employed in inflammatory conditions of the mouth and throat, but it is doubtful whether they are able to exert any significant antiseptic action in the way in which they are commonly used.

**EXPERIMENT 16. DISTRIBUTION OF A GARGLE.** Gargle with one mouthful of 0.01 per cent solution of methylene blue, and then reject the fluid. Observe the area of the mouth and throat which has been stained by the dye.

Illustrate your results by a drawing and comment upon them.

*N.B.* Methylene blue stains the teeth temporarily; students should bring a toothbrush with them to this meeting of the class.

### ACTION OF FERRIC CHLORIDE SOLUTION

Solution of ferric chloride has a mild antiseptic and a marked astringent action. It is a common constituent of mouth-washes.

**EXPERIMENT 17.** Rinse the mouth with 0.05 per cent solution of ferric chloride and describe the sensation which you experience.

*N.B.* Ferric chloride solution stains the teeth.

### ACTION OF ANTACIDS ON GASTRIC JUICE

The students should read the article on antacids in the National Formulary 1957, pp. 33-34 before starting these experiments.

The relative power of various commonly used antacids to

## DILLING'S CLINICAL PHARMACOLOGY

neutralise the hydrochloric acid of the gastric juice can be demonstrated *in vitro* with the acid of Universal indicator.

EXPERIMENT 18. To 2 ml. of dilute hydrochloric acid in each of three test tubes (*a*, *b* and *c*) add one drop of Universal indicator and note the pH.

Then add 65 mg. (weighed) of sodium bicarbonate to tube (*a*)

Then add 65 mg. (weighed) of magnesium oxide to tube (*b*).

Then add 65 mg. (weighed) of bismuth oxycarbonate to tube (*c*).

Note the alteration of pH and tabulate your results. Which is the most effective antacid? Why does the colour largely disappear from tube (*c*)?

EXPERIMENT 19. Take 2 ml. dilute hydrochloric acid and test with litmus paper. Add 65 mg. of magnesium trisilicate. Shake tube several times and after 5 minutes test with litmus paper (blue and red) again. Record and explain your results.

## ACTION OF HYALURONIDASE

Hyaluronidase is an enzyme which decreases the viscosity of certain tissue matrices. Its main therapeutic application is to increase the absorption of fluids injected into the subcutaneous tissues.

EXPERIMENT 20. Into the subcutaneous tissue of the right forearm inject normal saline solution, and note that as the volume injected reaches 2-3 ml. a large tense swelling begins to develop. When this swelling is beginning to become painful stop the injection and note the volume of saline injected. Measure the swelling and assess its tension by palpation. Repeat these observations every 5 minutes for 15 minutes and record them. Repeat the experiment in the opposite forearm, this time injecting the same quantity of normal saline solution to which hyaluronidase has been added (200 Benger units to the pint).

In what type of case would you consider using hyaluronidase?

**FIFTH MEETING****PRACTICAL PHARMACY****WEIGHTS AND MEASURES**

(See also footnote on p. 773).

**IMPERIAL SYSTEM**

<i>Solids.</i>	60 grains (gr.)	1 dram (dr.)
	8 drams	= 1 ounce (apothecaries') (oz.)
	1 apothecaries' ounce	= 480 gr.
	1 Imperial ounce	= 437·5 gr.
	(avoirdupois)	
<i>Liquids.</i>	60 minims (min.)	= 1 fluid dram. (fl. dr.)
	8 fl. dr.	= 1 fluid ounce (fl. oz.)
	20 fl. oz.	= 1 pint.

**APPROXIMATE EQUIVALENT METRIC AND IMPERIAL MEASURES**

<i>Solid.</i>	1 gr.	= 65 mg.	1 mg.	= 0·015 gr.
	dr.	= 4 G.	1 G.	= 15 gr.
	oz.	= 30 G.		
<i>Liquid.</i>	min.	= 0·06 ml.	1 ml.	= 17 m.
	fl. dr.	= 3·5 ml.	1 litre	= 35 fl. oz.
	1 fl. oz.	= 30 ml.		

**DOMESTIC MEASURES**

The capacity of domestic measures is usually given as follows:

1 teaspoonful	= 1 fl. dr.
1 dessertspoonful	= 2 fl. dr.
1 tablespoonful	= 4 fl. dr.
1 drop (e.g. from an eye-dropper)	= 1 m.

These figures are found to vary considerably in practice, and doses of potent medicines should always be measured accurately in a graduated medicine glass.



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EXPERIMENT 21. Each student should bring to the class:

- One domestic teaspoon.
- One domestic dessertspoon.
- One domestic tablespoon.
- One eye-dropper or pipette.

Calculate the capacity of each spoon in turn by using it to fill a 2 oz. measuring glass with water. Similarly with the pipette fill a one-dram measure and calculate the volume of one drop. Put your results on the blackboard. Copy the results of the other students, and in your laboratory notebook prepare a histogram of the results. Append your comments.

### PERCENTAGE SOLUTIONS

A percentage solution may be described as a weight-for-volume (w/v) solution, or as a volume-for-volume (v/v) solution. Thus a 10 per cent w/v solution of a solid or liquid is one which contains 10 G. of the solute made up with the solvent *to a total volume of* 100 ml. of the solution. Similarly a 10 per cent v/v solution of a liquid contains 10 ml. of the solute in a total volume of 100 ml. of the solution.

*Examples.* Injection of mersalyl contains 10 per cent w/v mersalyl and 5 per cent w/v theophylline.

Emulsion of liquid paraffin contains 50 per cent v/v of liquid paraffin.

In calculating percentage solutions in the Imperial System remember that: 1 fl. oz. of water = 480 min., weighs 437.5 gr. and therefore the volume of 100 gr. of water is:

$$\frac{480}{437.5} \times 100 \text{ m.} = 110 \text{ m. approximately.}$$

A 1 per cent w/v solution is therefore one which contains 1 gr. of the solid made up with water to 110 minims.

### APPLICATION OF DRUGS TO THE SKIN

In treating diseases of the skin the physician prescribes an active ingredient incorporated in a suitable base. The active

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ingredient may be an antiseptic, an astringent, an analgesic, an antipruritic, a rubefacient, a keratolytic or a detergent according to need. It is generally prescribed in low concentration, and often the physical properties of the vehicle in which the active drug is incorporated is of major importance. The following types of preparations will be considered here:

Poultices.  
Lotions.  
Liniments.  
Ointments.  
Pastes.  
Creams.

### STARCH POULTICE

This simple remedy is of value in softening and removing crusts on a heavily infected skin to allow of application of other remedies. It provides a convenient alternative to wet dressings aiming at maceration of the stratum corneum. If desired, a mild antiseptic may be incorporated as an active ingredient.

**EXPERIMENT 22. TO MAKE A STARCH POULTICE.** Take 30 G. starch. Mix into a smooth thick paste in a mortar with a little cold water. Quickly add 300 ml. of boiling water and stir vigorously with a pestle until the mixture sets to a thick jelly. When cool, spread poultice thickly on lint or muslin, cover with a thin layer of gauze, and bandage on to the back of your hand.

Record your experiences in your laboratory notebook. What is the mechanism of action of starch poultices? Would you use them in general practice? If so, for what conditions?

### LOTIONS

In a lotion the active drug, often an antiseptic, is dissolved or suspended in an aqueous base, e.g. Phenol lotion. Some lotions contain a volatile liquid, such as methylated spirit, which, by the evaporation, promotes cooling of the skin, e.g. Lead and Spirit Lotion.

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Glycerin is added to some lotions to prevent excessive drying of the skin. Some lotions contain insoluble ingredients in suspension, and, if evaporation is permitted, the solids—in fine particles—may continue to exert a therapeutic effect. Lotions are often used in the acute exudative phase of an inflammatory skin lesion. They help to wash away pus, debris and exudates, and they bring the active medicament into close contact with the inflamed part.

EXPERIMENT 23. Apply the following lotions to your skin:

Calamine lotion.  
Lead and spirit lotion.  
Zinc sulphate lotion.  
Tannic acid lotion.

Record the effects you experience as follows:

Ease of application.  
Cooling action.  
Astringent action.  
Persistence on skin.  
Duration of effect.  
Ease of removal.

Write out the formulæ of these lotions in your notebook, and state the reason for the inclusion of each ingredient. For what conditions would you use these lotions?

## LINIMENTS

Liniments or embrocations differ from ordinary lotions in that they contain soap or a fixed oil. The active ingredient is always an irritant or rubefacient, and the oil or soap is included to dissolve or emulsify the irritant substance, and to diminish friction when the liniment is *rubbed* on the skin.

EXPERIMENT 24. Apply the following liniments to an area of the skin, and note the following points:

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	Ease of application.
	Speed of "disappearance".
Methyl salicylate liniment	} Production of erythema, warmth, pain.
Turpentine liniment	
Camphor liniment	Duration of effect.
	Odour.

Write the formulæ of these liniments in your notebook and explain the presence of each ingredient. Would you use liniments in general practice? If so, for what conditions would you prescribe them?

## OINTMENTS, PASTES AND CREAMS

Like lotions, these consist of an active ingredient and a base. Here are some examples of suitable active ingredients for use in ointments, pastes and creams:

<i>Property</i>	<i>Drug</i>	<i>Concentration</i>
Antiseptic	Yellow oxide of mercury	1 per cent
Antibiotic	Chloramphenicol	2·5 per cent
Antipruritic	Coal tar	2 per cent
Counter-irritant	Capsicin	5 per cent
Keratolytic	Salicylic Acid	5 per cent

There are numerous available bases; these are pharmacologically inert, but possess important differences in their physical properties. The following properties are of particular importance in therapeutics:

- (i) Ease of application.
- (ii) Ease of removal.
- (iii) Emollient action.
- (iv) Degree of "stiffness".
- (v) Degree of greasiness.
- (vi) Degree of penetration of the skin.
- (vii) Heating or cooling effect on the skin.

EXPERIMENT 25. Test on yourself the properties of the following substances, often used in ointment bases, with respect to (i) to (vi) above:

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\*Paraffin wax (hard paraffin).

Yellow soft paraffin (Vaseline).

White soft paraffin.

Liquid paraffin.

\*Beeswax.

Hydrous wool fat (lanolin).

\* These must first be melted by gentle heat. Commonly used ointment bases are compounds, in varying proportions, of the above bases.

EXPERIMENT 26. Test the following, as in experiment 23:

Simple ointment.

Hydrous ointment.

Eye-ointment base.

Write the formulæ of these compound bases in your notebook.

### PASTES

These are made by adding a large quantity of inert powder, such as zinc oxide or starch, to an ointment base. Active ingredients may be added. Pastes may be used in the healing stages of exudative skin lesions. They are porous and cooling, and they are able to absorb exudate.

### CREAMS

These external applications resemble natural cream in that they are emulsions. There are two types of emulsion, water-in-oil and oil-in-water. In the usual type (oil-in-water) the active ingredient, dissolved in water, forms the aqueous or continuous phase. The oil, or dispersed phase, consists of a simple ointment base, such as a mixture of hard and liquid paraffin. The emulsion is made with the aid of emulsifying wax, a mixture of sodium salts of higher primary aliphatic alcohols.

DEMONSTRATION. The dispensing of:

(a) Zinc paste;

(b) Antazoline cream;

will be demonstrated.

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**EXPERIMENT 27.** Test the properties of zinc paste and of antazoline cream on your skin, and record your observations as in experiment 23. Write the formulæ of these two preparations and explain the function of each of the ingredients.

### *SIXTH MEETING*

Drugs to be taken by mouth are dispensed in the following forms:

*Solids.* Powders—individual or bulk.  
Compressed tablets—plain or sugar-coated.  
Pills.  
Capsules—ordinary or “enteric-coated”.  
Cachets.  
Lozenges.

*Liquids.* Mixtures.  
Emulsions.  
Elixirs.  
Syrups.  
Tinctures.

Most drugs are supplied in the form of tablets or capsules, each containing a single dose of the active drug. Prescribing these presents no difficulty. Several “ready-made” mixtures, elixirs, syrups and tinctures are also available and are often prescribed by name. The practitioner is most frequently called upon to prescribe a powder or a mixture.

### POWDERS

The following groups of drugs are the only ones frequently prescribed in the form of powders:

- (i) Antipyretics and analgesics.
- (ii) Antacids.
- (iii) A few purgatives.
- (iv) Drugs used in the symptomatic control of diarrhœa.

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Powders may contain one or several ingredients. Their only advantage over liquid mixtures is one of convenience.

When the total dose is small, and great accuracy of dosage is essential, individual powders are prescribed. These preferably should weigh 0.6–1.2 G. Lactose is used as a diluent, if necessary, to make the final size of the powder suitable. Powders should not be halved.

When the total dose is large and great accuracy is not essential, e.g. when antacids are prescribed, write bulk prescriptions. You waste the pharmacist's time by prescribing individual powders, and the cost is greater.

### MIXTURES

As with all prescriptions these consist simply of an active ingredient or ingredients and a base or vehicle. The prescriber requires to know only the dose of the active ingredient and its physical properties.

First write down the active ingredient or ingredients and the quantity required for a single dose, e.g.

Ferric Ammonium Citrate 2 G.

This substance (a) is freely soluble in water;

(b) does not deteriorate on standing.

Therefore, next state the amount of water to be added to give a single dose:

Ferric Ammonium Citrate 2 G.

Water to 8 ml.

The prescription is completed by adding the superscription and subscription in the usual way:

Ferric Ammonium Citrate 2 G.

Water to 8 ml.

Make a mixture. Send 180 ml.

Label: 2 teaspoonfuls three times a day in water after meals.

.....(1)

If there are two ingredients and both are soluble in water the form is the same, e.g.

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Sodium bicarbonate  
 Potassium citrate of each 1·3 G.  
 Water to 8 ml.  
 Make a mixture. Send 180 ml.

Label: 2 teaspoonfuls three times a day in water after meals.  
 .....(2)

If one, or more than one, of the active solid ingredients is insoluble in the vehicle but is relatively light, it is sufficient to prepare a *suspension*, with instructions to the patient to shake the bottle thoroughly before use, e.g.

Sodium bicarbonate 1·3 G.  
 Light magnesium carbonate 1·3 G.  
 Water to 8 ml.  
 Make a mixture. Send 180 ml.

Label: 2 teaspoonfuls three times a day in water after food.  
 Shake the bottle.  
 .....(3)

If, however, the insoluble ingredient is relatively dense, it cannot be satisfactorily dispersed throughout the mixture by shaking alone. It is now necessary to add to the mixture a *suspending agent*, usually *one* of the following:

<i>Suspending agent</i>	<i>Dose per fl. oz. of mixture</i>
Powdered tragacanth	60-120 mg.
Compound powder of tragacanth	0·6 G.
Mucilage of tragacanth	4-8 ml.
Acacia powder	4 G.

(Acacia is seldom used because of the large quantity required),  
 c.g.

Chalk 1·3 G.  
 Powdered tragacanth 30 mg.  
 Water to 8 ml.  
 Make a mixture. Send 180 ml.

Label: 2 teapoonfuls every 4 hours in water.  
 Shake the bottle.  
 .....(4)



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EXPERIMENT 28. Inspect and taste simple mixtures (1), (2) (3) and (4). Describe in your notebook their appearance, flavour and consistence, and indicate the amount of shaking necessary to render them homogeneous. What is the practical importance of the last point?

If one or more of the active ingredients is a liquid, this is usually freely miscible with the vehicle, and no difficulty arises, e.g.

Ammonium chloride	1 G.
Aromatic solution of ammonia	0.6 ml.
Liquid extract of liquorice	1 ml.
Water to	8 ml.

Rarely the liquid ingredients may be immiscible with the vehicle, e.g. if an oil is prescribed. It is then necessary to make an emulsion.

### PRESERVATIVES

In a few prescriptions it is necessary to add a preservative to prevent deterioration of the mixture. A well-known example of this:

Ferrous sulphate	90 mg.
Dilute hypophosphorous acid	0.0125 ml.
Dextrose	1 G.
Water to	4 ml.
Make a mixture.	Send 180 ml.

Label: 1 teaspoonful three times a day.

### FLAVOURING AGENTS

The flavour of some, but not all, mixtures can be improved by choice of a suitable flavouring agent. The selection of the best agent in any particular case is a matter of experience and preference. Flavouring agents are *dilute* or *concentrated*. The dilute agents are the following:

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Chloroform water.  
Camphor water.  
Aniseed water.  
Cinnamon water.  
Peppermint water.  
Infusion of quassia.

These are used, in place of plain water, as the vehicle for the mixture, e.g.

Ferric Ammonium Citrate 2 G.  
Chloroform water to 8 ml.  
Make a mixture. Send 180 ml.

Label: 2 teaspoonfuls three times a day in water after meals.

The concentrated flavouring agents contain aromatic substances—usually volatile oils from fruit or vegetable sources—and they may be available as aromatic waters, tinctures, syrups, etc., e.g.

Glycerin.	Oil of peppermint.
Simple syrup.	Oil of anise.
Syrup of orange.	Oil of camphor.
Syrup of ginger.	Oil of cinnamon.
Syrup of tolu.	Liquid extract of liquorice.
Syrup of wild cherry.	Infusion of quassia (bitter).

These are added to the mixture in a small dose. Note that as a rule only one flavouring agent is necessary in the mixture, e.g.

- |     |                             |         |
|-----|-----------------------------|---------|
| (a) | Potassium citrate           | 3 G.    |
|     | Citric acid                 | 0.6 G.  |
|     | Syrup of Ginger             | 4 ml.   |
|     | Water to                    | 15 ml.  |
| (b) | Potassium iodide            | 150 mg. |
|     | Liquid extract of liquorice | 1 ml.   |
|     | Water to                    | 8 ml.   |

EXPERIMENT 29. You are provided with three mixtures, A B and C, and three flavouring agents X, Y and Z. Taste each mixture first unflavoured, then after addition of each flavouring

agent in turn. Record your opinions of the taste of each, and state what you consider to be the most suitable flavouring agent for each of the mixtures supplied.

### SYRUPS AND LINCTUSES

These are merely mixtures containing large quantities of syrup as demulcent and flavouring agents.

EXPERIMENT 30. Taste the following and record your impressions:

Syrup of codeine phosphate.  
Linctus of codeine.  
Compound syrup of figs.

### EMULSIONS

Unpleasant oily preparations such as cod-liver oil and liquid paraffin can be made more palatable by emulsifying them with water, using acacia or tragacanth as the emulsifying agent. In making such an emulsion with one of these fixed oils, the oil, water and acacia are first mixed in the proportion 4:2:1. This *primary emulsion* is diluted to the required strength by adding more water.

EXPERIMENT 31. Compare the taste of the following pairs of compounds:

- (a) Liquid extract of cascara sagrada *and* Elixir of cascara sagrada.
- (b) Cod-liver oil *and* Emulsion of cod-liver oil.
- (c) Liquid paraffin *and* Emulsion of liquid paraffin.

EXPERIMENT 32. Dispense the following prescription:

Preparation of weak solution of Iodine—"Tincture" of iodine  
Liquor Iodi Mitis.

**R**      Iodine                      2·5 G.  
         Potassium Iodide 2·5 G.  
         Distilled Water    2·5 ml.  
         Alcohol 90 per cent to 100 ml.

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*Dispensing note.* Dissolve potassium iodide and iodine in the distilled water. Add sufficient alcohol to make the required volume.

### EXPERIMENT 33. Dispense:

Mr. -----.                      Date.

**R**                      Chalk                      0·6 G.  
                         Powdered tragacanth 30 mg.  
                         Tincture of opium    0·3 ml.  
                         Cinnamon water to    8 ml.  
                         Make a mixture: Send 60 ml.

Label: 2 teaspoonfuls when necessary. Shake the bottle.

*Dispensing note.* Mix the chalk and tragacanth in the mortar; add about half the total volume of Cinnamon water and triturate. Dilute the tincture of opium with equal volume of Cinnamon water; add to contents of mortar and triturate. Adjust with Cinnamon water to the required volume.

## SEVENTH MEETING

At this meeting you will make the lotion, liniment, powder and mixtures for which you have already written prescriptions. In your notebook describe the following:

1. The formula of each compound and the reason for the inclusion of each ingredient.
2. The method you employed to compound the mixture, etc.
3. The appearance, consistence, colour and (when applicable) taste of your compound.

Would you be prepared to prescribe the compounds you have now made for the treatment of your patients?

Simplicity in prescribing makes medical practice less complicated for the doctor and treatment less hazardous for the patient.

## TERMS USED IN PRESCRIPTION WRITING

The physician's directions to the pharmacist (in the "Subscription" to the list of drugs) have traditionally been written in Latin. A further convention that has been widely adopted is to abbreviate these Latin words—often to the point of using only initial letters. Thus a kind of shorthand has been invented. It has created many difficulties in the past and in some circumstances abbreviations create unnecessary danger. In this context it is therefore best to regard all these Latin words and abbreviations as obsolete. The younger practitioner may, however, be called upon to decipher such terms in prescriptions, and a list of Latin words formerly used in prescription writing is given for reference in the following pages.

## WEIGHTS

(See also footnote to p. 773)

<i>Latin</i>	<i>Contraction</i>	
Granum	gr.	grain
Uncia	oz.	ounce (437.5 gr.)
Semigranum	½ gr. (gr.ss.)	half a grain
Granum dimidium		
Grani dimidium	1½ gr. (gr.ss.)	grain and half
Granum cum semisse		
Grani quadrans	¼ gr.	quarter of a grain
Quarta pars grani		

## MEASURES

Minimum	m.	minim
Uncia fluida	fl. oz.	fluid ounce (480 m.)

The following traditional symbols are *not* now recommended for use in prescription writing: *their equivalents in grains, minims or ounces should be employed.*

Scrupulum (scruple)		20 grains
Drachma (drachm)	(dr.)	60 grains

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Uncia (ounce)		437·5 grains or 1 ounce (avoir.)
Drachma fluida (fluid drachm)	(fl. dr.)	60 m.
Uncia fluid (fluid ounce)	(fl. oz.)	480 m. or 1 fl. oz.

### APPROXIMATE (DOMESTIC) MEASURES

While liquid preparations are often conveniently administered in teaspoonful, dessertspoonful or tablespoonful doses, it is to be emphasised that spoons vary greatly in capacity. Medicines should be measured in measures graduated in minims and fluid ounces.

Gutta	gtt.	drop, $\frac{1}{2}$ -2 m.
Cochleare parvum minimum	coch. parv.	teaspoonful, 60 m.
Cochleare medium medicum	coch. med.	dessertspoonful, 120 m.
Cochleare amplum magnum	coch. mag.	tablespoonful, $\frac{1}{2}$ fl. oz.
Cyathus Vinarius	C. Vin.	wineglassful, 2-3 fl. oz.
Cyathus Magnus	C. Mag.	tumblerful, 10 fl. oz.
Peculum	Pcc.	teacupful, 5-6 fl. oz.

*Latin Terms and Abbreviations.* The use of these by students is not recommended; English should be used. The lists given are for reference to explain contractions met with in prescriptions in textbooks, etc.

### INSTRUCTIONS TO DISPENSER

<i>Latin</i>	<i>Contraction</i>	<i>English</i>
ad	ad.	to, up to
Ad libitum	ad lib.	at pleasure
Adde	add.	add
Ana	aa	of each
Da, detur	d.	give, let be given
Divide	div.	divide

## DILLING'S CLINICAL PHARMACOLOGY

<i>Latin</i>	<i>Contraction</i>	<i>English</i>
Fiat; Fiant	ft.	let be made
Habeat	hab.	let him have
Misce	m.	mix
Mitte	mitt.	send
Quantum sufficiat	} q.s.	sufficient
Quantum Satis		
Recipe	<b>R</b>	take
Repete	repet.	repeat
Secundum artem	s.a.	in the proper way: with pharmaceutical skill
Signa, Signetur	Sig.	label, let it be labelled.
Solve	solve	dissolve
Talis, tales talia	tal.	such

## FORMS OF ADMINISTRATION

Capsula amylacea	caps. amylac.	cachet
Capsula gelatina	caps. gelat.	gelatin capsule
Cataplasma	cataplasma.	a poultice
Collunarium	collunar.	a nasal douche
Collutorium	collut.	a mouth-wash
Collyrium	collyr.	an eye lotion
Confectio	conf.	a confection
Embrocatio	embroc.	an embrocation
Emplastrum	emp.	a plaster
Emulsio	emul.	an emulsion
Enema	enem.	an enema
Gargarisma	garg.	a gargle
Gelatinum	gelatin.	a gelatin
Haustus	hst.	a draught
Inhalatio	inhal.	an inhalation
Injectio	inj.	an injection
Insufflatio	insuff.	an insufflation
Lamella	lamell.	a disc.
Linimentum	lin.	a liniment
Lotio	lot.	a lotion

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Massa	mass.	a mass
Mistura	mist.	a mixture
Nebula	neb.	a spray
Oculentum	oculent.	an eye ointment
Pasta	past.	a paste
Pessus	pess.	a pessary
Pigmentum	pigm.	a paint
Pilula	pil.	a pill
Pulvis	pulv.	a powder
Solvella	solv.	a solution-tablet
Suppositorium	suppos	a suppository
Tabella	tab.	a tablet
Tabletta	tab.	a tablet
Trochiscus	troch.	a lozenge
Ungentum	ung.	an ointment
Vapor	vapor	an inhalation
Vinum	vin.	a wine.

## INSTRUCTIONS FOR PATIENT

It is recommended that instructions for patients should be written in English. However, the following terms were formerly in use and are included here for the student's information.

Admoveantur	admov.	apply, let it be applied.
Ante cibos	a.c.	before meals
Applicetur	applic.	let it be applied
Bis in die	b.i.d.	twice a day
Capiat	cap.	let him take, let . . . be t:
Capiantur		
Cum cibo (cibis)	c̄.c.	with food (meals)
Decubitus hora	decub.hor.	at bedtime
Ex aqua	ex.aq.	in water
Febri durante	feb. dur.	during the fever
Mane	m.	in the morning
More dicto	m.d.	as directed
Nocte	n.	at night
Partes æquales	p.æ.	equal parts, weights.



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Post cibum (cibos)	p.c.	after food (meals)
Quaque quarta hora	q.q.h.	every four hours
Si opus sit	s.o.s.	if necessary
Statim	stat.	immediately
Ter in die	t.i.d.	thrice a day
Ter die sumendus	t.d.s.	to be taken three times a day

# APPENDIX IV

## PHARMACEUTICAL CHEMISTRY

### THE NOMENCLATURE OF DRUGS

THE arbitrary manner in which drugs are named is a source of confusion and frustration to students of pharmacology, pharmacy and medicine. A situation already complex enough is complicated even further by the fact that many drugs possess more than one name in common use, to say nothing of the various trade names under which they may be marketed. Even optical isomers may possess individual names which serve only to obscure their extremely simple relationship to one another. An example is provided by *atropine* which is the racemic form of hyoscyamine. Further, there is no international agreement on the naming of drugs, and the unfortunate consequence is that the various pharmacopœias each compile their own lists of "approved names". Thus, in different parts of the world official recognition may be given to different names though they refer to the same drug. The circumstances inevitably produce a state of chaos entirely foreign to a scientific discipline, and students are thus all too easily discouraged from reading widely because of the additional effort required to recognise the compounds concerned and to correlate the information to be obtained.

Again it is the practice in some laboratories which synthesise and test new drugs to assign a serial number to each new compound prepared; and it often happens that the new substance is given a name only after it has shown promise on clinical trial. If writers fail to quote the serial number alongside the new name, scientific work is inevitably hindered. A comprehensive survey of the literature relating to a chemical compound can be made only when all its designations are known.

There is, unfortunately, little that can be done to improve the present state of drug nomenclature and it remains necessary

to commit to memory details of the chemical structure of a drug and its various names and numbers. In the light of this situation this chapter is intended to make the naming of drugs as intelligible as possible and to help the student to determine the chemical structure of a drug from a knowledge of its chemical name.

The names of drugs can often be traced to various trivial circumstances, though such names are usually modified to a greater or lesser degree by elements of the systematic nomenclature of organic chemistry. If the drug happens to be obtained from natural sources, the name often reflects the source from which it was first isolated. Not only are crude extracts and preparations such as those of digitalis and belladonna named in this way, but frequently the purified active principle is assigned a name obviously akin to that of its source—for example strychnine (from *Strychnos nux-vomica*), cocaine (from *Erythroxylon coca*), colchicine (from *Colchicum autumnale*), cortisone (from the adrenal cortex) and penicillin (from *Penicillium notatum*). Cholesterol was first isolated from gallstones and derives its name from the Greek *chole* = bile and *steros* = solid.

Sometimes synthetic compounds also have names originally derived from the name of a plant. The salicylates are an example, for salicylic acid was first prepared from the glycoside salicin which occurs in the bark of the common willow (*Salix alba*).

Another practice (which often has unforeseen consequences) is to attempt to confer on drugs names which indicate their actions and therapeutic uses. Thus, as opium often causes drowsiness, morphine is named after Morpheus, the Greek god of dreams; and picrotoxin is so-named from its use by the natives of the East Indies as a fish poison. Antabuse which is used to combat alcoholism is another example. Pituitary growth hormone and oxytocin are examples of nomenclature according to function.

Where the name of a drug is rather long it is not uncommon to use a contracted form. Sometimes this shortened form includes portions of a full name as in the case of nalorphine for N-allyl-normorphine and in other instances initial letters are employed as with TEPP for tetraethylpyrophosphate, BAL for British anti-lewisite and ACTH for adrenocorticotrophic hormone. A most undesirable form of contraction which is all too often employed

involves the omission of the numerals showing the position of the substituents in a systematic name. Such abbreviations serve only to defeat the advantages of systematic nomenclature. Examples are diphenylhydantoin for 5:5-diphenylhydantoin\*, di-iodohydroxyquinoline for 8-hydroxy-5:7-di-iodoquinoline and tribromoethanol for 2:2:2-tribromoethanol.

With the object of securing the widest possible market for their products, manufacturers spend much time and show much ingenuity in devising short acceptable names which are easily remembered and which can be patented. The use of trade names should be avoided if possible in medical practice. Such names must of course be known in order to ascertain what preparations of a particular drug have been made available by various manufacturers; and, conversely, to ascertain the nature of the drugs present in proprietary preparations. It may be recalled that because the accepted BP name, *Adrenaline*, very closely resembles a trade name, the USP has adopted the official name Epinephrine instead.

As with trade names, many of the BP approved names are artificially coined, and may bear no obvious relationship to the systematic name of the drug, as for example with methadone which is 2-dimethylamino-4:4-diphenylheptan-5-one. On infrequent occasions a trivial name bears considerable resemblance to the systematic name, perhaps the most inspired example being tuaminoheptane for 2-aminoheptane!

The systematic nomenclature of organic chemistry is very complex and it is not proposed to summarise it here. Rather, the present account is designed as an explanatory guide to common usage, whether this be strictly correct or not, in order to enable the medical student to understand the chemical names of the drugs most likely to be encountered. Unfortunately the relatively complex chemical structure of many drugs in common use makes such simplified treatment rather superficial.

\* While this book was in press the British convention was changed to bring it into line with American practice. Commas are now used in place of colons between the numbers showing the position of the substituents in a systematic name. Thus 5:5-diphenylhydantoin is in future to be written 5,5-diphenylhydantoin.

Many of the chemically complex compounds such as the protein hormones, and some of the vitamins and antibiotics are invariably referred to by trivial names as application of systematic nomenclature to these substances would result in very long and unwieldy names.

The first serious attempt to place the nomenclature of organic compounds on a systematic footing had its origin in the recommendations of the International Congress at Geneva in 1892. However, as more complicated organic molecules became known the Geneva system was found to be inadequate, and current nomenclature is based fundamentally on the Definitive Report of the Committee for the Reform of Nomenclature in Organic Chemistry published in *Comptes rendus* of the 10th Conference (Liège) of the International Union of Chemistry 1930 (*J. Chem Soc.*, 1931, 1607) and in *Comptes rendus* of the 12th Conference (Lucerne and Zürich) IUC 1936. Revision and expansion of these rules are made periodically by the International Union of Pure and Applied Chemistry.

For a full account of systematic nomenclature the student should consult R. S. Cahn: *An Introduction to Chemical Nomenclature* (London: Butterworth, 1959) and the Editorial Reports on Nomenclature which are issued annually by the Chemical Society.

Excellent summaries of the rules of systematic nomenclature are to be found in *The Extra Pharmacopœia* (Martindale), vol. II, 23rd Edition, pp. 754-76 (1955), and in the various editions of the *Handbook of Chemistry and Physics* published by the Chemical Rubber Publishing Co., Cleveland, Ohio.

The nomenclature of organic compounds normally employs a substitutive terminology: a given compound is described in terms of a certain fundamental structure in which hydrogen atoms are considered to have been replaced by other atoms or groups of atoms (radicals). The fundamental molecules which bear the basic names are the alkane hydrocarbons, certain cyclic and polycyclic compounds and several other substances possessing specialised atomic groupings. In order to indicate which hydrogen atoms of the fundamental structure are so replaced by other atoms or radicals, each fundamental molecule is assigned a numbering system which must be learnt along with the chemical

structure. Many radicals are formally derived from the fundamental molecules by the loss of hydrogen atoms. In such cases the radical is assigned a name derived from the name of the parent compound by certain changes of suffix. It is thus necessary to consider the fundamental structures most likely to be encountered in the molecules of therapeutic compounds and their names, together with those of the common radicals.

### A. THE ALKANES

The alkanes are hydrocarbons belonging to the series whose formulæ can be expressed generically as  $C_nH_{2n+2}$ . Their names are derived from the Greek or Latin numeral corresponding to the number of carbon atoms in the molecule with the addition of the suffix "ane". Important exceptions are the first four members of the series, methane, ethane, propane and butane whose names do not involve numerals. Although the alkanes themselves are of little therapeutic value, a large number of drugs possess names derived from those of the alkanes, and consequently it is necessary to know the names of the lower members. Accordingly the names of the first twenty alkane hydrocarbons are listed in Table I.

TABLE I

#### ALKANE HYDROCARBONS

<i>Name</i>	<i>Formula</i>	<i>Name</i>	<i>Formula</i>
Methane	$CH_4$	Undecane	$C_{11}H_{24}$
Ethane	$C_2H_6$	Dodecane	$C_{12}H_{26}$
Propane	$C_3H_8$	Tridecane	$C_{13}H_{28}$
Butane	$C_4H_{10}$	Tetradecane	$C_{14}H_{30}$
Pentane	$C_5H_{12}$	Pentadecane	$C_{15}H_{32}$
Hexane	$C_6H_{14}$	Hexadecane	$C_{16}H_{34}$
Heptane	$C_7H_{16}$	Heptadecane	$C_{17}H_{36}$
Octane	$C_8H_{18}$	Octadecane	$C_{18}H_{38}$
Nonane	$C_9H_{20}$	Nonadecane	$C_{19}H_{40}$
Decane	$C_{10}H_{22}$	Eicosane	$C_{20}H_{42}$

For members possessing four or more carbon atoms isomerism is possible as the carbon atoms can be linked in straight chains or branched chains. The methods of naming the branched-chain

members will not be discussed here except to say that all branched-chain derivatives can be named as substituted derivatives of the longest chain in the molecule.

To illustrate the application of substitutive nomenclature in the alkanes we shall use as examples compounds bearing simple substituents. The simplest substituents are those which consist of a single atom or of various inorganic radicals, and the most commonly encountered examples are given in Table II.

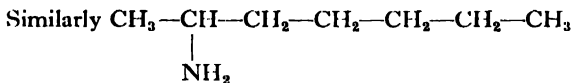
TABLE II

## SIMPLE SUBSTITUENTS

Name	Formula	Name	Formula
Amino	—NH <sub>2</sub>	Cyano	—CN
Arsino	—As—As—	Fluoro	—F
Bromo	—Br	Hydroxy	—OH
Carbamoyl	—C(=O)—NH <sub>2</sub>	Iodo	—I
		Mercapto	—SH
	O	Mercuri	—Hg—
Chloro	—Cl	Nitro	—NO <sub>2</sub>
Chloromercuri	—HgCl	Sulphonamido	—SO <sub>2</sub> —NH <sub>2</sub>

The lines beside the grouping represent the free valency bonds by which the grouping is attached to the body of the molecule.

The compound CH<sub>3</sub>CH<sub>2</sub>Cl is known as chloroethane as it represents the fundamental compound ethane in which one hydrogen atom has been replaced by a chlorine atom.



is known as 2-aminoheptane. The prefixing numeral indicates which carbon atom bears the amino group. For all alkanes the numbering of the carbon chain starts at one end of the longest straight chain possible and continues to the other end. Which end is chosen as carbon atom number one is determined by the rule that the smallest possible numbers are always to be employed in designating the position of the substituents. In the present example if the numbering had been started from the other end the name would have been 6-aminoheptane which involves the use of a higher number. The method of specifying carbon atom number six is to

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write it as C-6 or C<sub>(6)</sub>. If a compound contains six carbon atoms it is often termed a C<sub>6</sub> compound.

Where the same substituent occurs more than once in the molecule this is indicated by the use of the prefixes "di", "tri", "tetra" "penta", "hexa", etc. Thus the compound ClCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Cl is called 1:3-dichloropropane and the compound CH<sub>3</sub>CH<sub>2</sub>CHCl<sub>2</sub> is 1:1-dichloropropane. Similarly cadaverine H<sub>2</sub>N—(CH<sub>2</sub>)<sub>5</sub>—NH<sub>2</sub> is 1:5-diaminopentane.

### SYSTEMS DERIVED FROM THE ALKANES

(a) *Simple Organic Radicals*. Where an organic radical can be regarded as being formed from an alkane by the loss of a hydrogen atom it is known as an alkyl radical and as this generic term indicates, the names of the individual radicals are formed by replacing the terminal "ane" in the name of the parent hydrocarbon by the suffix "-yl". Thus the methyl radical is formally related to methane by the loss of a hydrogen atom, the ethyl radical to ethane, and so on. An important exception is the radical containing five carbon atoms which continues to be called the amyl radical despite recommendations to replace this name by the name pentyl radical. The common alkyl radicals are included in Table III.

TABLE III

#### SIMPLE ORGANIC RADICALS

<i>Name</i>	<i>Formula</i>
<i>Straight Chain</i>	
Methyl	CH <sub>3</sub> —
Ethyl	CH <sub>3</sub> CH <sub>2</sub> —
nPropyl	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> —
nButyl	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> —
nAmyl (pentyl)	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> —
nHexyl	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> —

#### *Branched Chain*

<i>iso</i> Propyl	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>CH-}$
<i>iso</i> Butyl	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>CHCH}_2$

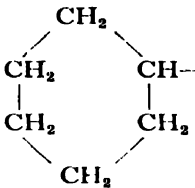
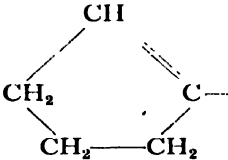
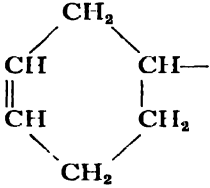
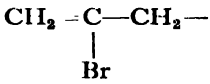
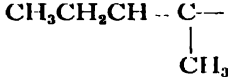


TABLE III (continued)

<i>Name</i>	<i>Formula</i>
<i>sec</i> Butyl	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3 \end{array} \text{CH}—$
<i>tert</i> Butyl	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} \text{C}—$
<i>iso</i> Amyl	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CHCH}_2\text{CH}_2—$
<i>tert</i> Amyl	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3 \\ \text{CH}_3 \end{array} \text{C}—$
1-Methylbutyl	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}— \\   \\ \text{CH}_3 \end{array}$
<i>Alkenyl Radicals</i>	
Vinyl	$\text{CH}_2=\text{CH}—$
Allyl	$\text{CH}_2=\text{CH}-\text{CH}_2—$
2-Butenyl	$\text{CH}_3-\text{CH}=\text{CH}-\text{CH}_2—$
<i>Alkynyl Radicals</i>	
Ethynyl	$\text{CH}-\text{C}—$
Propargyl	$\text{CH}-\text{C}-\text{CH}_2—$
<i>cycloAlkyl Radicals</i>	
<i>cyclo</i> Propyl	$\begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2—\text{CH}— \end{array}$
<i>cyclo</i> Butyl	$\begin{array}{c} \text{CH}_2-\text{CH}- \\   \quad   \\ \text{CH}_2-\text{CH}_2 \end{array}$
<i>cyclo</i> Pentyl	$\begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}- \\   \quad   \\ \text{CH}_2-\text{CH}_2 \\ \diagdown \quad \diagup \\ \text{CH}_2 \end{array}$

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TABLE III (continued)

<i>Name</i>	<i>Formula</i>
cycloHexyl	
cycloAlkenyl Radicals	
1-cycloPentenyl	
3-cycloHexenyl	
<i>Common Substituted Radicals</i>	
Hydroxymethyl	HOCH <sub>2</sub> —
Chloromethyl	ClCH <sub>2</sub> —
Trifluoromethyl	CF <sub>3</sub> —
Dibromomethyl	CHBr <sub>2</sub> —
2-Bromallyl	
1-Methyl-1-butenyl	
<i>Polymethylene Radicals</i>	
Ethylene	—CH <sub>2</sub> —CH <sub>2</sub> —
Trimethylene	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> —
Tetramethylene	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> —
Pentamethylene	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> —
Hexamethylene	—(CH <sub>2</sub> ) <sub>6</sub> —

Where an alkyl radical possesses three or more carbon atoms isomerism is possible because chain branching can occur. Customarily where no indication to the contrary is given, it is assumed that it is the straight chain form to which reference is made. Occasionally, however, in order to stress the fact that the radical is straight chain, the name is prefixed by *n* (standing for normal) as in the *n* hexyl radical, the *n* octyl radical and so on. The simpler branched-chain alkyl radicals, are given common names and these are listed in Table III. For the more complex branched-chain radicals this method of nomenclature is no longer adequate and such radicals are themselves regarded as substituted derivatives of the longest chain present. One such radical which occurs in certain of the barbiturates is the 1-methylbutyl radical shown in the table. In the case of branched-chain radicals named in this way the carbon atom attached to the rest of the molecule is invariably designated carbon atom number one.

Where a double bond is introduced into an alkyl radical an alkenyl radical is formed. The two simplest alkenyl radicals which are also the two most commonly encountered have irregular names and are known as the vinyl and allyl radicals. Their formulæ are shown in Table III. In the larger alkenyl radicals it is necessary to indicate the position of the double bond and this is done by giving the number of the carbon atom after which the double bond occurs as in the example of the 2-butenyl radical shown in the table. Where no such number is given the double bond follows carbon atom number one.

Radicals possessing a triple bond are known as alkynyl radicals. These are of infrequent occurrence as substituents in drug molecules. The two simple examples which have irregular names, viz. the ethynyl and propargyl radicals, are the only members of this series likely to be encountered.

Where a hydrocarbon is formally derived from an alkane by ring formation with the loss of two hydrogen atoms it is termed a *cycloalkane* and the corresponding radical is known as a *cycloalkyl* radical. The most common *cycloalkyl* radicals are shown in Table III.

It is common practice when portraying structural formulæ of molecules to show the rings of cyclic and polycyclic compounds without writing in the carbon atoms and the hydrogen atoms attached to them. The rings are drawn as regular geometrical figures, triangles, squares, pentagons, hexagons, etc., and so it is easy to tell at a glance whether the ring contains 3, 4, 5, 6, etc.,

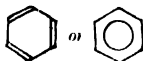
## PHARMACEUTICAL CHEMISTRY

carbon atoms. Substituents are shown and hydrogen atoms too when they have special stereochemical significance. Thus a plain hexagon represents a *cyclohexane* molecule, every angle representing a carbon atom. Each line represents the bond between two adjacent carbon atoms and it is understood that every carbon atom bears as many hydrogen atoms as are necessary to bring its valencies up to four. In the case of the unsubstituted *cycloalkanes* there are two hydrogen atoms on each carbon atom. The same principle applies to alkyl substituents attached to the ring. A single short stroke

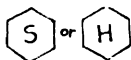
represents a methyl group as in methyl*cyclobutane*

Care must be taken not to confuse this convention with that of showing the free valency bonds occurring in the *cycloalkyl* radicals. For this reason *cycloalkyl* radicals are best depicted in the manner used in Table III. Longer alkyl groups attached to rings are drawn as zig-zag lines. Each angle represents a carbon atom, once again having attached as many hydrogen atoms as are necessary to bring its total valencies up to four.

To distinguish benzene rings from *cyclohexane* rings the former are always drawn as



and *cyclohexane* rings are occasionally drawn as



S standing for saturated and H for hydrogenated.

The same convention of not showing carbon atoms and the hydrogen atoms attached to them is also used in the case of heterocyclic compounds, i.e. compounds which have an atom of an element other than carbon incorporated in the ring system. Here the hetero atom is of course portrayed as in pyrrolidine



Hydrogen atoms attached to such hetero atoms are also shown.

Examples of polycyclic molecules drawn in this manner are to be found in Table XII in the section dealing with steroid nomenclature.

There are also *cycloalkenyl* radicals. As in the case of the *alkenyl* radicals the position of the double bond is indicated by giving the number of the carbon atom after which it occurs.

Alkyl radicals can themselves be substituted and several examples are included in Table III.

One other type of simple organic radical which may be encountered is the group known collectively as the *polymethylene* radicals. These radicals have two free valencies, one at each end of a straight chain of carbon atoms. Examples are included in Table III. Thus cadaverine  $\text{H}_2\text{N}(\text{CH}_2)_5\text{NH}_2$  can be named pentamethylene diamine.

(b) *Ethers*. The simple ethers are usually named according to the two radicals attached to the oxygen atom. A list of the ethers of importance in anaesthesia together with their chemical formulæ is given in Table IV. It is to be noted that where the two radicals are the same the prefix "di" is commonly omitted. Thus diethyl ether and divinyl ether are usually referred to simply as ethyl ether and vinyl ether respectively.

TABLE IV

ETHERS

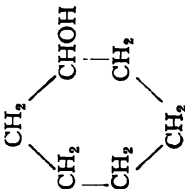
Diethyl ether	$\text{CH}_3\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_3$
Divinyl ether	$\text{CH}_2=\text{CH}-\text{O}-\text{CH}=\text{CH}_2$
Vinylisopropyl ether	$\text{CH}_2=\text{CH}-\text{O}-\text{CH}\begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$
2:2:2-Trifluoroethylvinyl ether	$\text{CF}_3\text{CH}_2-\text{O}-\text{CH}=\text{CH}_2$

(c) *Alcohols*. The alcohols are characterised by the possession of an OH group which is known as the hydroxyl group or alcoholic function. Three forms of nomenclature are still commonly employed. These are the additive nomenclature, the Geneva nomenclature and the systematic substitutive nomenclature.

In the additive nomenclature alcohols are named according to the radical present followed by the word alcohol. Examples are given in Table V.

TABLE V

ALCOHOLS

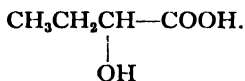
Formula	Additive Nomenclature	Geneva Nomenclature	Substitutive Nomenclature
$\text{CH}_3\text{OH}$	Methyl Alcohol	Methanol (Carbinol)	
$\text{CH}_3\text{CH}_2\text{OH}$	Ethyl Alcohol	Ethanol	
$\text{CH}_3\text{CH}_2\text{CHOH}$ $\text{CH}_3$	secButyl Alcohol	2-Butanol	
$\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$	Allyl Alcohol	Prop-2-en-1-ol	3-Hydroxypropene
$\text{CH}_3\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)_2$	tertAmyl Alcohol	2-Methylbutan-2-ol	2-Hydroxy-2-methylbutane
	cycloHexyl Alcohol	cycloHexanol	

It is to be noted that *tert* amyl alcohol is frequently described as "amylene hydrate" but this designation is obsolete.

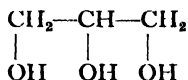
The Geneva nomenclature names an alcohol according to its parent hydrocarbon by replacing the terminal "e" by the suffix "-ol". For example methane is considered to give rise to methanol by replacement of a hydrogen atom with a hydroxyl group.

In cases where ambiguity can arise, the position of the alcoholic function must be indicated. This can be done in three ways. The number can precede the name as in 2-butanol; it can come before the functional name as in butan-2-ol; or it can follow the word as in butanol-2. Where another function is also present, however, as in allyl alcohol (the double bond) care must be taken to show clearly which number refers to which function and so prop-2-en-1-ol is the least ambiguous form. Where no number is indicated the hydroxyl group is on carbon atom number one.

The substitutive systematic nomenclature is not commonly used in the case of simple alcohols where the Geneva system is advocated. It is used in more complex molecules especially where other functions are present as for example in the hydroxy acids. This method of nomenclature is exemplified by 1-hydroxybutyric acid,



Where two hydroxyl groups are present in the molecule the compound can be named as a diol and where there are three as a triol. Glycerin,

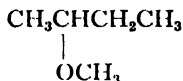


is thus known as propan-1:2:3-triol. An alcohol containing two hydroxyl groups is known as a dihydric alcohol, an alcohol with three hydroxyl groups as a trihydric alcohol and so on.

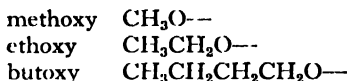
In highly substituted alcohols it is common to regard the other substituents as replacing hydrogen atoms of the parent alcohol. Thus the compound  $\text{CBr}_3\text{CH}_2\text{OH}$  which is formed by the replacement of three hydrogen atoms in the ethanol molecule is correctly termed 2:2:2-tribromoethanol. As by employing the term ethanol the alcoholic group is by convention considered to be on carbon atom number one; the bromine atoms are on carbon atom number two.

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Where the hydrogen atom of the hydroxyl group is replaced by alkyl groups an alkoxy radical results. Alkoxy radicals are used substitutively to name the more complex ethers, as for example 2-methoxy butane,

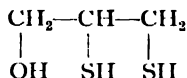


Examples of alkoxy radicals are



Similarly the radical  $\text{CH}_2=\text{CH}-\text{CH}_2\text{O}-$  is known as the allyloxy radical.

(d) *Thiols*. These compounds are characterised by the possession of an  $-\text{SH}$  group variously known as the mercapto, sulphhydryl or thiol group. They are named in a strictly analogous fashion to the alcohols, although the IUC has recommended that the additive form of nomenclature in which the compound is termed an alkyl mercaptan, as for example ethyl mercaptan,  $\text{C}_2\text{H}_5\text{CH}_2\text{SH}$ , be abandoned. This compound should be termed ethanethiol instead, by adding the suffix "thiol" to the name of the parent compound ethane. In the substitutive method the SH group is termed mercapto. The substitutive terminology is properly reserved for molecules already possessing other substituents. Thus BAL (British anti-lewisite),



is called 2:3-dimercaptopropanol. Once again the alcoholic function is considered as the first substituent by naming the compound as a propanol derivative.

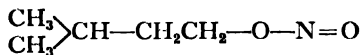
(e) *Esters of Inorganic Acids*. These are named as if they were alkyl salts of the acid.

Thus *isoamyl nitrite* is derived from nitrous acid by replacement of the acidic hydrogen of the acid which is analogous to replacement of the acidic hydrogen by sodium ion, for example in the formation

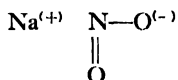


## DILLING'S CLINICAL PHARMACOLOGY

of sodium nitrite. The important difference is of course that *isoamyl nitrite*,



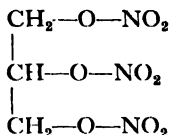
is a covalent compound, whereas sodium nitrite,



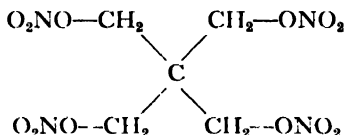
is an ionic compound.

Similarly the esters of other inorganic acids such as nitric acid, sulphuric acid and phosphoric acid are known as nitrates, sulphates, phosphates and so on.

Where the ester is formed from a polyhydric alcohol the number of alcoholic groups which are esterified are indicated by the prefixes, di, tri, etc., before the acid radical name. Examples are glyceryl trinitrate,



and erythritol tetranitrate,



(f) *Amines*. Amines are characterised by the possession of a trivalent nitrogen atom. Where the nitrogen atom bears one hydrocarbon radical and two hydrogen atoms (that is, the  $-\text{NH}_2$  group is present) the compound is known as a primary amine. Where there are two hydrocarbon substituents and one hydrogen atom it is termed a secondary amine, and where the nitrogen atom bears three hydrocarbon substituents it is called a tertiary amine. However, where an organic substituent is an acyl radical (see below) the compound is known as an amide. Alkaloids are naturally occurring complex amines or amine salts and to show their amine nature they are given names ending in "ine".

Amines are commonly named by both an additive and a substitutive nomenclature.

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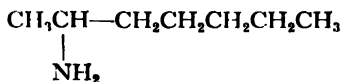
In the additive system the names of all the radicals attached to the nitrogen atom are given followed by the word amine. Where the same radical occurs more than once the prefixes "di" and "tri" are used as applicable. The alkyl radicals are correctly named in alphabetical order as is always true for the name of any substituted molecule bearing more than one substituent. For alphabetical purposes prefixes in italics are neglected and *cyclohexyl* for example is considered to come under the letter H. Examples of common amines named in this manner are given in Table VI.

### TABLE VI

#### AMINES

Methylamine	$\text{CH}_3\text{NH}_2$
Dimethylamine	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>NH}$
Ethylmethylamine	$\text{CH}_3\text{CH}_2\text{NH}-\text{CH}_3$
Dipropylamine	$\text{CH}_3\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_3$
Triethylamine	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3\text{CH}_2 \end{array} \text{>N}-\text{CH}_2\text{CH}_3$
Ethylcyclohexylamine	$  \begin{array}{c}  \text{CH}_3 \\  \diagup \quad \diagdown \\  \text{CH}_2 \quad \text{CH}-\text{NH}-\text{CH}_2\text{CH}_3 \\    \quad   \\  \text{CH}_2 \quad \text{CH}_2 \\  \diagdown \quad \diagup \\  \text{CH}_2  \end{array}  $

In the substitutive nomenclature which is of greater flexibility the compound is named as an amino derivative of the parent compound, as for example 2-aminoheptane,



In the substitutive nomenclature secondary and tertiary amines are named by employing substituted amino radical names as for example:

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Methylamino	$\text{CH}_3\text{NH—}$
Dimethylamino	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>N—}$
Ethylmethylamino	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3 \end{array} \text{>N—}$

Several substituted amino-substituted alkyl radicals frequently occur in the molecules of chemical compounds used as drugs and these are listed below. The logical derivation of the names is readily apparent.

(2-Dimethylaminoethyl)	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{>N—CH}_2\text{CH}_2\text{—}$
(2-Diethylaminoethyl)	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3\text{CH}_2 \end{array} \text{>N—CH}_2\text{—CH}_2\text{—}$
(3-Diethylaminopropyl)	$\begin{array}{c} \text{CH}_3\text{CH}_2 \\ \text{CH}_3\text{CH}_2 \end{array} \text{>N—CH}_2\text{CH}_2\text{CH}_2\text{—}$

As many amines are sparingly soluble in water they are often administered in the form of soluble salts. These are named by an additive nomenclature using the full name of the amine, followed by the derived acid name. Thus we speak of 2-aminoheptane hydrochloride, adrenaline tartarate, morphine sulphate and so on.

(g) *Quaternary Salts of Amines.* These are named as substituted ammonium salts.

For example  $[(\text{CH}_3)_4\text{N}]^{(+)}\text{I}^{(-)}$  is tetramethylammonium iodide and  $[(\text{CH}_3\text{CH}_2)_4\text{N}]^{(+)}\text{OH}^{(-)}$  is tetraethylammonium hydroxide.

(h) *Halogen Derivatives.* As with the alcohols and amines both substitutive and additive systems of nomenclature are commonly employed. Thus chloroethane is also referred to as ethyl chloride. The ending "o" to the name of a halogen atom always signifies substitutive nomenclature, the ending "ide" additive nomenclature.

The general anæsthetic trichloroethylene,  $\text{CHCl}=\text{CCl}_2$ , is therefore regarded as being formed from the ethylene molecule by the replacement of three hydrogen atoms by three chlorine atoms.

(i) *Aliphatic Carboxylic Acids.* The aliphatic carboxylic acids are closely related to the alkanes and are characterised by the possession of the  $\text{—COOH}$  group which is known as the carboxyl group. The systematic names of these compounds are derived from the names of the corresponding alkanes by changing the suffix—"ane" to

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—“anoic” acid, but nearly all the acids encountered in pharmacology and medicine are so common that they possess trivial names. A list of the most frequently encountered carboxylic acids is given in Table VII. The list includes certain common substituted acids having trivial names.

TABLE VII

## CARBOXYLIC ACIDS

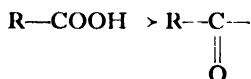
Name	Formula
Formic acid	$\text{HCOOH}$
Acetic acid	$\text{CH}_3\text{COOH}$
Propionic acid	$\text{CH}_3\text{CH}_2\text{COOH}$
Butyric acid	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$
Valeric acid	$\text{CH}_3(\text{CH}_2)_3\text{COOH}$
Caproic acid	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$
Caprylic acid	$\text{CH}_3(\text{CH}_2)_6\text{COOH}$
Palmitic acid	$\text{CH}_3(\text{CH}_2)_{11}\text{COOH}$
Stearic acid	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$
Oxalic acid	$\text{HOOC}-\text{COOH}$
Malonic acid	$\text{HOOCCH}_2\text{COOH}$
Succinic acid	$\text{HOOC}(\text{CH}_2)_2\text{COOH}$
Glutaric acid	$\text{HOOC}(\text{CH}_2)_3\text{COOH}$
Adipic acid	$\text{HOOC}(\text{CH}_2)_4\text{COOH}$
Glycollic acid	$\text{HOCH}_2\text{COOH}$
Lactic acid	$\text{CH}_3\text{CH}(\text{OH})\text{COOH}$
Tartaric acid	$\text{HOOC}-\text{CH}(\text{OH})-\text{CH}(\text{OH})-\text{COOH}$
Citric acid	$\begin{array}{c} \text{HOOC}-\text{CH}_2-\text{C}(\text{OH})-\text{CH}_2\text{COOH} \\   \\ \text{COOH} \end{array}$
Acrylic acid	$\text{CH}_2=\text{CHCOOH}$
Undecylenic acid	$\text{CH}_2=\text{CH}-(\text{CH}_2)_8\text{COOH}$
Glycine	$\text{NH}_2\text{CH}_2\text{COOH}$
Glucuronic acid	

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Where a carboxylic acid occurs as a salt the ending is changed from "ic" to "ate" as in sodium caprylate, zinc undecylenate, adrenaline tartarate, calcium citrate, etc. The same ending "ate" is employed where an ester of the acid is involved. The radical present in the alcohol from which the ester is formed is used to complete the name of the ester as in ethyl acetate  $\text{CH}_3\text{COOCH}_2\text{CH}_3$ , methyl caprylate  $\text{CH}_3(\text{CH}_2)_6\text{COOCH}_3$ , etc.

In some cases where the alcohol is very complex and has a trivial name, the name of the alcohol itself, not that of a derived radical, is used. Examples are cortisol acetate and testosterone propionate.

Radicals formally derived from organic carboxylic acids by the loss of the OH from the carboxyl group, viz.

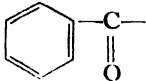



are generically known as acyl radicals. Their names are formed by changing the terminal "ic" of the name of the corresponding acid to the suffix "yl".

Examples of commonly encountered acyl radicals are given in Table VIII.

### TABLE VIII

#### ACYL RADICALS

<i>Formula</i>	<i>Name</i>	<i>Parent acid</i>
$\text{H}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-$	formyl	$\text{HCOOH}$ formic acid
$\text{CH}_3-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-$	acetyl	$\text{CH}_3\text{COOH}$ acetic acid
$\text{CH}_3\text{CH}_2-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-$	propionyl	$\text{CH}_3\text{CH}_2\text{COOH}$ propionic acid
	benzoyl	 $\text{COOH}$ benzoic acid

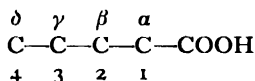
## PHARMACEUTICAL CHEMISTRY

Where an acyl radical is joined to an amino group an amide results. An example is acetamide  $\text{CH}_3\text{CONH}_2$ . The derived radical  $\text{CH}_3\text{CONH}-$  is frequently encountered and is known as the acetamido radical.

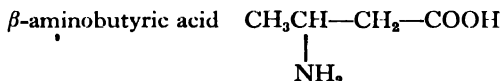
Where a radical is derived by the loss of a hydrogen atom from the carboxyl group and not an OH group, the derived radical is named by replacing the terminal "-ic" of the name of the acid by "-oxy". Examples are :

$\text{CH}_3\text{COO}-$	acetoxy radical
$\text{CH}_3\text{CH}_2\text{COO}-$	propionoxy radical
$\text{CH}_3\text{CH}_2\text{CH}_2\text{COO}-$	butyroxoy radical

The numbering of the carbon chain in an aliphatic carboxylic acid varies according to the system of nomenclature employed in naming the acid. Where the acid has a trivial name or the name ends in "carboxylic acid" as for example in butane carboxylic acid, the carbon atom which bears the carboxylic function is designated 1 or  $\alpha$ . The numbering or lettering then proceeds regularly along the carbon chain away from the carboxylic group, thus :



Substituents can then be unambiguously assigned as, for example,



Where the ending "anoic" acid occurs the carbon atom of the carboxyl group is called number one, the adjacent carbon atom number two, and so on.

In complex molecules the following groups are occasionally employed in substitutive terminology,

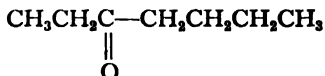
Carboxy	$-\text{COOH}$
Methoxycarbonyl or Carbomethoxy	$-\text{COOCH}_3$
Ethoxycarbonyl or Carbethoxy	$-\text{COOCH}_2\text{CH}_3$

(j) *Ketones*. Ketones are characterised by the grouping  $\begin{array}{c} -\text{C}- \\ || \\ \text{O} \end{array}$

which is attached to two organic radicals. This C=O grouping is known as the carbonyl, keto or oxo group. Systematically ketones

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are named by replacing the terminal "e" in the name of the parent compound by "one" as in 3-heptanone (heptan-3-one),



although the additive form of nomenclature is also used (ethyl butyl ketone). Acyl radicals are commonly employed in naming the more complex ketones and utilising this terminology the above compound would be named as 1-propionyl butane. In the substitutive nomenclature the same example would be called 3-ketoheptane or 3-oxoheptane.

(k) *Sulphones*. Sulphones are characterised by the grouping  $\text{—SO}_2\text{—}$  attached to two organic hydrocarbon radicals. Usually an additive form of nomenclature is employed using the name of the radicals as in methyl ethyl sulphone  $\text{CH}_3\text{SO}_2\text{CH}_2\text{CH}_3$  or diethyl sulphone  $\text{CH}_3\text{CH}_2\text{SO}_2\text{CH}_2\text{CH}_3$ .

## B. ACYCLIC MOLECULES POSSESSING FUNDAMENTAL NAMES

Very few acyclic molecules possessing fundamental names are commonly encountered. Those most likely to be concerned in drug nomenclature are:

Urea	$\text{H}_2\text{NCONH}_2$
Isourea	$\text{H}_2\text{N—C=NH}$   $\text{OH}$
Urethane	$\text{H}_2\text{NCOOCH}_2\text{CH}_3$
Guanidine	$\text{H}_2\text{N—C—NH}_2$    $\text{NH}$
Semicarbazide	$\text{H}_2\text{NNHCONH}_2$
Thiosemicarbazide	$\text{H}_2\text{NNHC(S)NH}_2$
Hydrazine	$\text{H}_2\text{NNH}_2$

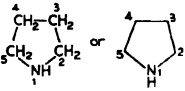


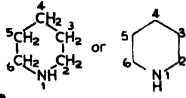


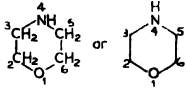


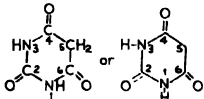
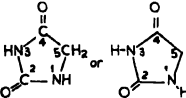
The derivatives of semicarbazide and thiosemicarbazide formed by interaction with the carbonyl group of another molecule are known as semicarbazones and thiosemicarbazones. The radical  $\text{H}_2\text{NNH—}$  formed from hydrazine is known as the hydrazino radical.

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## C. FUNDAMENTAL NON-AROMATIC HETEROCYCLIC COMPOUNDS

Several representatives of this class of compound are frequently encountered as constituents of drug molecules and these are listed in Table IX. The numbering of the ring systems is given and the names of the derived radicals are also listed. Unfortunately some heterocycles have been assigned different numbering systems at different times in their history which leads to some confusion. Usually, however, the numbering commences at the hetero atom.

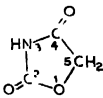
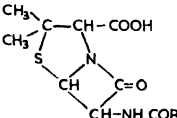
TABLE IX

<i>Name</i>	<i>Formula</i>	<i>Name of Derived Radical</i>	<i>Formula</i>
Pyrrolidine		'Pyrrolidino	
		2-Pyrrolidinyl	
Piperidine		Piperidino	
		2-Piperidinyl	
Morpholine		Morpholino	
		3-Morpholinyl	
Barbituric Acid			
Hydantoin			



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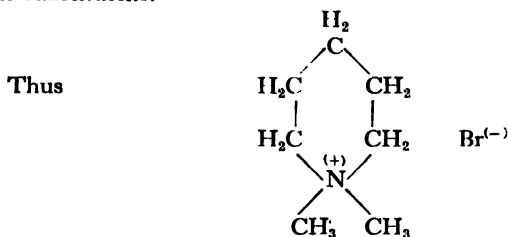
## TABLE IX (continued)

Name	Formula
Oxazolidine-2:4-dione	
General formula of the penicillins	

Actually pyrrolidine and oxazolidine-2:4-dione are not fundamental names, but they are listed here as such for convenience.

It is to be noted that heterocyclic nitrogen-containing compounds such as pyrrolidine, piperidine and morpholine form radicals which are named differently according to whether the free valency bond is on the nitrogen atom or on a carbon atom. Where it is on the nitrogen atom the ending "ino" is used to correspond to the amino radicals. Where it is on a carbon atom the ending "inyl" is used to correspond to the alkyl radicals. In the case of the "inyl" radicals it is necessary to indicate the number of the carbon atom which bears the free valency to avoid ambiguity.

Where a quaternary salt is formed on a nitrogen atom incorporated in a ring system, the name is evolved by changing the terminal "-ine" of the fundamental name into "inium" and indicating the substituents.



is 1:1-dimethyl piperidinium bromide.

Barbituric acid is shown in the table but unfortunately the clinical names of the commonly used barbiturates are not derived systematically as substituted barbituric acid derivatives. Moreover separate names often exist for the sodium salts which are formed by

## PHARMACEUTICAL CHEMISTRY

displacement of hydrogen ions from the nitrogen atoms by sodium ions.

Also included in Table IX is the general formula of the penicillins. The letter R stands for the various radicals occurring in the different penicillins. Thus where R is benzyl we have benzylpenicillin.

### D. NON-HETEROCYCLIC AROMATIC COMPOUNDS

The fundamental non-heterocyclic aromatic compounds are the parent hydrocarbons in which all the carbon atoms are incorporated in rings. But as many of the more common derivatives possess trivial names, the more important of these are included along with the fundamental compounds in Table X. The radicals

TABLE X


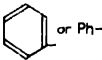
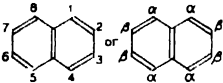


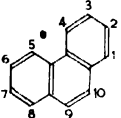





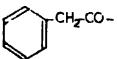
<i>Name</i>	<i>Formula</i>	<i>Name of Derived Radical</i>	<i>Formula</i>
Benzene		Phenyl	
Naphthalene		1-Naphthyl ( <i>α</i> -Naphthyl)	
		2-Naphthyl ( <i>β</i> -Naphthyl)	
Phenanthrene			
Toluene		Benzyl	
		<i>o</i> -Tolyl	
		<i>m</i> -Tolyl	
		<i>p</i> -Tolyl	
		Toluyl	

TABLE X (continued)






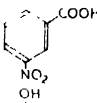


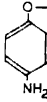
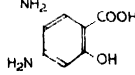

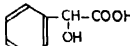
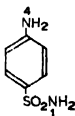
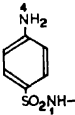

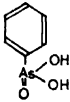






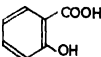

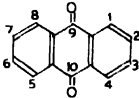
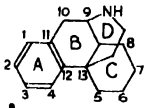
Name	Formula	Name of Derived Radical	Formula
Chlorobenzene		<i>o</i> -Chlorophenyl	
		<i>m</i> -Chlorophenyl	
		<i>p</i> -Chlorophenyl	
<i>o</i> -Dichlorobenzene			
<i>m</i> -Nitrobenzoic acid		<i>m</i> -Nitrobenzoyl	
<i>p</i> -Aminophenol		<i>p</i> -Aminophenoxy	
4-Amino-2-hydroxybenzoic acid ( <i>p</i> -Aminosalicylic acid)			
Catechol ( <i>o</i> -Dihydroxybenzene)			
Mandelic acid			
Sulphanilamide ( <i>p</i> -Aminobenzene sulphonamide)		N <sup>1</sup> -Sulphanilamido	
Benzene sulphonic acid			
Benzene arsonic acid			

TABLE X (continued)

Name	Formula	Name of Derived Radical	Formula
Phenol		Phenoxy	
Aniline		Anilino	
Benzoic acid		Benzoyl	
Salicylic acid		Benzoyloxy	
Anthraquinone			
Morphinan			

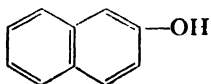
shown in the table are frequently encountered and the student of pharmaceutical chemistry is expected to commit them to memory. Aromatic compounds not possessing trivial names are assigned names by substitutive nomenclature in a fashion strictly analogous to that already described for non-aromatic compounds. An example is chlorobenzene.

Where there are two substituents on a benzene ring the *ortho*, *meta*, *para* nomenclature is commonly employed. Where one substituent is on the carbon atom adjacent to the carbon atom bearing the other substituent the two substituents are said to be in the *ortho* relationship to each other. An example is afforded by *ortho* dichlorobenzene. The word *ortho* is customarily abbreviated to *o*. The substituents are said to be in the *meta* or *m* relationship when the carbon atoms bearing them are separated by one carbon atom bearing no substituents as in the case of *meta* nitrobenzoic acid. The prefix *para* or *p* indicates that the carbon atoms bearing the two

## DILLING'S CLINICAL PHARMACOLOGY

substituents are separated by two unsubstituted carbon atoms. An example is *p*-aminophenol.

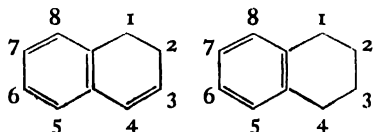
The *o*, *m*, *p* terminology is also occasionally applied to cyclohexane (hexahydrobenzene) and is carried over to phenyl radicals bearing one substituent such as the tolyl radicals and the chlorophenyl radicals shown in Table X, but it is not used for any aromatic hydrocarbons other than those possessing a benzene ring. When three or more substituents are involved in the benzene series their positions are best indicated by number as is the case for the naphthalene, phenanthrene and other polycyclic series no matter what the number of substituents. Simple naphthalene derivatives, however, are still differentiated by using letters of the Greek alphabet, for example  $\beta$ -naphthol ( $\alpha$ -naphthol)



In the more complex aromatic structures the rings are designated by capital letters. This has been done in Table X for the compound morphinan which can be considered as the parent compound from which morphine is derived. With the advent of the new synthetic morphine derivatives it was found necessary to assign morphinan the role of a fundamental compound to facilitate the naming of the new derivatives.

Where aromatic systems are partially reduced (or hydrogenated) an additive nomenclature is employed in which hydrogen atoms are considered to have been added to the carbon atoms concerned.

Thus the compounds



are known as 1:2-dihydro-naphthalene and 1:2:3:4-tetrahydro-naphthalene respectively. The prefixes dihydro, tetrahydro, hexahydro, etc., always indicate such addition of hydrogen atoms and must not be confused with the term dehydro which is sometimes used to indicate that a compound is related to its parent compound by the loss of a molecule of hydrogen. The term "anhydro" is occasionally used to show that a compound is formally derived from a parent structure by the loss of a molecule of water, a hy-

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drogen atom and an OH group on adjacent carbon atoms having been abstracted.

### E. AROMATIC HETEROCYCLIC COMPOUNDS

These are compounds in which an atom other than carbon is incorporated in the aromatic ring system. Table XI lists the most important members together with their derived radicals.

TABLE XI




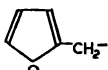
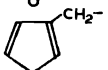






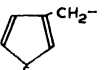
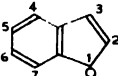
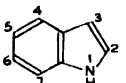
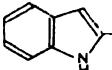



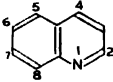
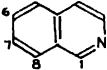
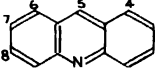


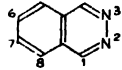
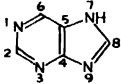

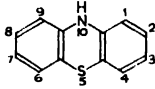
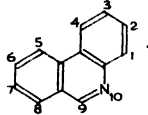


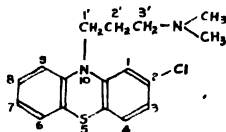
<i>Name</i>	<i>Formula</i>	<i>Name of Derived Radical</i>	<i>Formula</i>
Furan		2-Furyl	
		3-Furyl	
		2-Furfuryl	
		3-Furfuryl	
Pyrrole	 or 	2-Pyrryl	
Thiophen	 or 	2-Thienyl or $\alpha$ -Thienyl	
		3-Thenyl or $\beta$ -Thenyl	
Benzofuran			
Indole		2-Indolyl	
Pyridine	 or 	3-Pyridyl or $\beta$ -Pyridyl	

TABLE XI (continued)

Name	Formula	Name of Derived Radical	Formula
Quinoline			
Isoquinoline			
Acridine			
Pyrimidine		2-Pyrimidyl	
Phthalazine			
Purine			
Thiazole			
Phenothiazine			
Phenanthridine			
Imidazole		5-Imidazolyl	

## F. COMPLEX MOLECULES WITH COMPLEX SUBSTITUENTS

In the case of certain complex molecules, to show the derivation from the parent compounds it is sometimes necessary to number both the main portion of the molecule and the side chain. In such cases it is usual to assign ordinary numerals to the nucleus and numerals bearing superscript dashes to the side chain. An example is afforded by chlorpromazine,



which is systematically named as 2-chloro-10-(3'-dimethylamino-propyl) phenothiazine.

The brackets are used to avoid ambiguity: all that comes inside the brackets is substituted at position 10 of the phenothiazine nucleus.

Many compounds of therapeutic value are named in this way.

## G. STEROID NOMENCLATURE

The steroids are a large group of compounds possessing a complex chemical structure. Many steroids occur naturally and it is customary to divide the group into several subclasses of which the bile salts, the cardiac glycosides, the vitamins D, the male and female sex hormones and the hormones of the adrenal cortex are of importance in medicine. The naturally-occurring steroids of therapeutic value all possess trivial names, but with the introduction into medicine of numerous synthetic steroids of value in hormonal therapy it becomes necessary for the student to know something of the way in which these synthetic compounds are named. Unfortunately steroid nomenclature has been in a state of flux over the past few years, but with the approval of definitive rules for the nomenclature of steroids by the International Union of Pure and Applied Chemistry at Paris in 1957, it is anticipated that uniform nomenclature will be achieved at last.

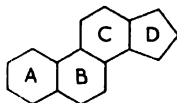
Because much of the current literature still employs older ter-



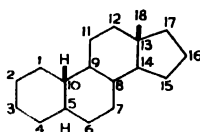
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minology all the alternative fundamental names likely to be encountered in the naming of steroid hormones are indicated in Table XII. All steroid hormones can be named from the six fundamental hydro-

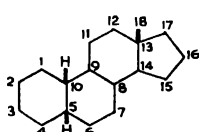
### TABLE XII



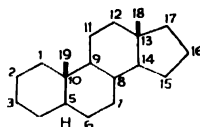
#### Perhydrocyclopentenophenanthrene



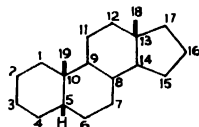
**5α-Estrane**



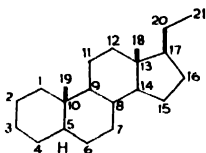
**5β-Estrane**



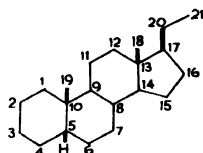
**5α-Androstane  
or Androstane**



**5β-Androstane  
or Ætiocholane  
or Testane**



**5α-Pregnane  
or Allopregnane**



**5β-Pregnane  
or Pregnane**

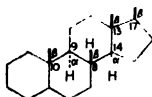
carbons, whose structural formulæ together with the numbering systems are shown in the table. Also shown is the perhydrocyclopentenophenanthrene system which forms the fused tetracyclic ring system or nucleus of the steroid molecule. Steroids are not usually named as substituted perhydrocyclopentenophenanthrene

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derivatives as this name is too long and clumsy to employ as a fundamental name, but possession of the perhydrocyclopentenophenanthrene system or minor modifications of it is the criterion by which a compound is classed as a steroid. The individual rings are assigned letters as shown and the same ring lettering applies to the fundamental steroid hydrocarbons. It is to be noted that three rings A, B and C are six-membered whilst the fourth ring, ring D, is five-membered. The steroid nucleus is drawn in the manner described earlier for simple cyclic systems. Each angle represents a carbon atom and each line represents the bond between two adjacent carbon atoms. It is understood that every carbon atom bears as many hydrogen atoms as are necessary to bring its valencies up to four. Stereochemistry is extremely important in the steroid series and so hydrogen atoms are shown where they have a special stereochemical significance. This is particularly true of the hydrogen atom on carbon atom number five.

Valency bonds projecting above the plane of the steroid nucleus are said to possess the  $\beta$  configuration and are indicated as heavy lines, whilst valency bonds projecting below the nucleus are said to possess the  $\alpha$  configuration and are represented by broken lines. Where the hydrogen atom on C-5 has the  $\alpha$  configuration the steroid molecule is said to have a trans A/B ring junction. Such steroids are sometimes referred to as the allo steroids, a usage reflected in the obsolete name allopregnane. Current usage is to indicate the configuration of the hydrogen atom at C-5 as in 5 $\alpha$ -pregnane, 5 $\alpha$ - $\alpha$ -estrane and 5 $\alpha$ -androstane. Where the hydrogen atom on C-5 has the  $\beta$  configuration the steroid molecule is said to possess a cis A/B ring junction. Such steroids are sometimes referred to as the normal steroids. Current nomenclature names the fundamental compounds as 5 $\beta$  compounds as in 5 $\beta$ - $\alpha$ -estrane, 5 $\beta$ -androstane and 5 $\beta$ -pregnane.

Variation in the stereochemistry at all carbon atoms in the steroid nucleus is of course possible, and the isomers are specified by use of the  $\alpha$  and  $\beta$  nomenclature. It is understood, however, that the stereochemistry at C-8, C-9, C-10, C-13, C-14 and C-17 is always as below unless specification is made to the contrary.

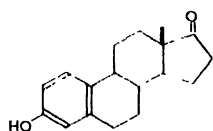


## DILLING'S CLINICAL PHARMACOLOGY

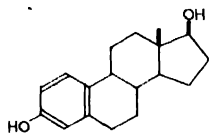
As the steroidal oestrogens all possess an aromatic ring A (i.e. they are benzene derivatives) they can be regarded as derivatives of either  $5\alpha$ -oestrane or  $5\beta$ -oestrane as the stereochemistry at C-5 does not have to be taken into account. The chemical structures of some of the steroidal oestrogens are shown in Table XIII. It is to be noted that the configuration of the hydroxyl group in oestradiol - $17\beta$  and of the ethinyl group in  $17\alpha$ -ethinyloestradiol is indicated by using the  $\alpha\beta$  convention.

The male sex hormones can be regarded as derivatives of  $5\alpha$ -androstane and  $5\beta$ -androstane whose older names are androstane and aetiocholane or testane respectively. The more common male sex hormones are shown in Table XIV. It is to be noted that the

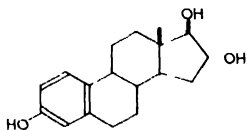
TABLE XIII  
OESTROGENS



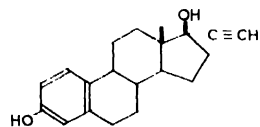
Oestrone  
or 1:3:5-oestratriene-3-ol-17-one



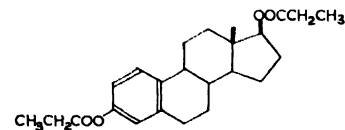
Oestradiol- $17\beta$   
or Oestradiol  
or 3:17β-Dihydroxyoestra-1:3:5-triene



Estriol  
or 3:16α:17β-Trihydroxyoestra-1:3:5-triene



$17\alpha$ -Ethinylestradiol  
or Ethinylestradiol

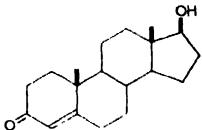
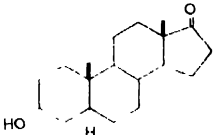
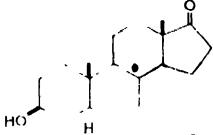
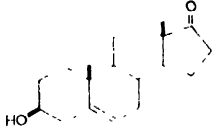
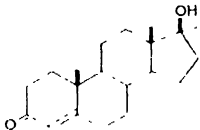
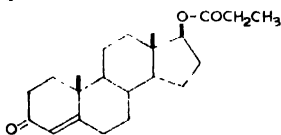


Oestradiol dipropionate

## PHARMACEUTICAL CHEMISTRY

names testosterone and androsterone are used as subsidiary basic names. *Epi*androsterone and androsterone differ only in the configuration at C-3. Dehydroepiandrosterone is more accurately designated as 5-dehydroepiandrosterone as this defines the position of the double bond. Because androsterone has a ketone function at C-17 it belongs to the class known as the 17-ketosteroids. The synthetic gestogen ethisterone (17 $\alpha$ -ethinyl testosterone) is also an androstane derivative.

### TABLE XIV

	Testosterone or 17 $\beta$ -Hydroxy-3-keto-androst-4-ene.
	Androsterone or 3 $\alpha$ -Hydroxy-17-keto-5 $\alpha$ -androstane
	<i>Epi</i> androsterone or 3 $\beta$ -Hydroxy-17-keto-5 $\alpha$ -androstane
	5-Dehydroepiandrosterone or 3 $\beta$ -Hydroxy-17-keto-androst-5-ene.
	17 $\alpha$ -Methyltestosterone
	Testosterone propionate

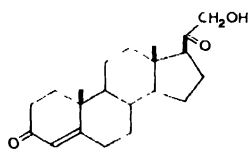
D.C.P.—28\*

## DILLING'S CLINICAL PHARMACOLOGY

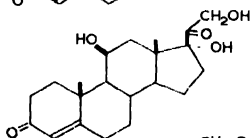
The hormones of the adrenal cortex and the natural gestogen, progesterone, are derivatives of the basic hydrocarbons  $5\alpha$ -pregnane and  $5\beta$ -pregnane as is the new general anæsthetic 21-hydroxy- $5\beta$ -pregan-3:20-dione sodium succinate.

### TABLE XV

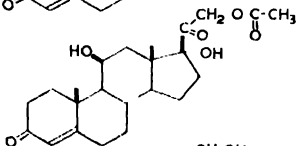
#### ADRENOCORTICAL HORMONES



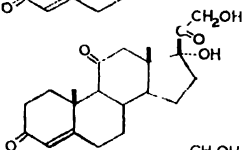
Deoxycorticosterone  
or Deoxycortone  
(21-hydroxy-3:20-dioxopregn-4-ene)



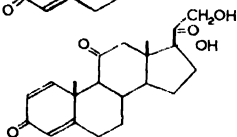
Cortisol  
or Hydrocortisone  
(3:20-dioxo-11 $\beta$ :17 $\alpha$ :21-trihydroxypregn-4-ene)



Hydrocortisone acetate



Cortisone  
(17 $\alpha$ :21-dihydroxy-3:11:20-triketopregn-4-ene)



Prednisone  
or deltacortisone  
(17 $\alpha$ :21-dihydroxy-3:11:20-triketopregn-1:4-diene)

The most common of the adrenocortical hormones are shown in Table XV. It is to be noted that deoxycortone derives its name from the compound cortone (or corticosterone) which has a hydroxyl group on C-11. Hydrocortisone is so named because it differs from cortisone by having the 11-keto function reduced to an alcoholic function (i.e. formal addition of one molecule of hydrogen to the

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carbonyl group). Fludrocortisone or 9 $\alpha$ -fluorohydrocortisone differs from hydrocortisone by the substitution of a fluorine atom in the 9 $\alpha$  position.

Numerous other synthetic steroid hormones are known, but the above examples should suffice to illustrate the principles of their systematic nomenclature. If the student understands these principles he should have no trouble in determining the chemical structure of the newer synthetic steroids. Some of these are named as 19-norpregnane derivatives, which means they are formally derived from pregnane by the loss of carbon atom number 19.

The  $\text{—C—CH}_2\text{OH}$  side chain, characteristic of some of the



steroids of the adrenal cortex is sometimes known as the  $\alpha$ -ketol side chain. It is to be emphasised that the term  $\alpha$  here does not refer to configuration but indicates that the keto group and hydroxyl group are on adjacent carbon atoms (C-20 and C-21).

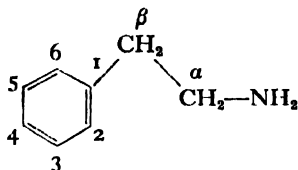
## H. PREFIXES

Finally there are certain commonly used prefixes which are encountered in the names of compounds used as drugs which call for brief comment.

*O and N.* The capital letters O and N before the name of a substituent as in O-acetylphenol or N-methyl adrenaline indicate that the substituent is attached to the oxygen atom and the nitrogen atom respectively. Such terminology can be employed only in cases where there is no ambiguity. This is true in the above examples, as there is only one oxygen atom in phenol and only one nitrogen atom in adrenaline.

$\alpha$ ,  $\beta$ ,  $\gamma$ , etc. These Greek letters are used to indicate different things and need to be interpreted strictly in context.

As already indicated, they are commonly used to denote the position of substituents as in the case of substituted aliphatic carboxylic acids, and in the older nomenclature for certain derivatives of naphthalene, pyridine, thiophen, etc. They are also occasionally used to denote the position of substituents in other systems, a surviving example being the  $\beta$ -phenylethylamine derivatives which are considered derivatives of the structure



where the carbon atoms of the side-chain are designated  $\alpha$  and  $\beta$  as shown. Also  $\alpha$  and  $\beta$  have a similar significance in the names acetyl- $\alpha$ -methylcholine and acetyl- $\beta$ -methylcholine.

The letters  $\alpha$ ,  $\beta$ ,  $\gamma$ , etc., are also used to indicate stereoisomers where the exact stereochemistry is unknown, or was not known when the names were assigned. Examples are the synthetic analgesics  $\alpha$ -methadylacetate and  $\beta$ -methadylacetate which are stereoisomeric,  $\beta$ -erythroidine, and  $\gamma$  benzene hexachloride—the insecticide which is one of a number of stereoisomers.

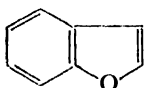
$\alpha$  and  $\beta$  have stereochemical significance in sugar chemistry and may be encountered in the naming of glycosides (complex sugar derivatives).

In steroid nomenclature the terms  $\alpha$  and  $\beta$  have a strict significance and indicate whether a substituent lies below or above the plane of the ring system.

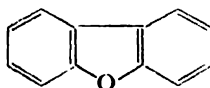
**Benzo.** The prefix benzo is used to indicate that a compound is related to its parent by the addition of a fused benzene ring. Examples are benzofuran and dibenzofuran.



Furan



Benzofuran



Dibenzofuran

**Bis.** Literally, *bis* means taken twice, and is used in various contexts. Where a complex radical already involving the prefix *di* occurs twice in a molecule the word *bis* is used to indicate this. Thus *bis* (1:1-dimethylbutyl) amine is preferable to *di* 1:1-dimethylbutylamine.

The term is also used to describe compounds having two quaternary nitrogen atoms in the molecule such as the polymethylene *bis*-trimethylammonium salts,



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and the *bis* isoquinolinium salts of which tubocurarine is an example. The polymethylene *bis*—*isothiour*eas afford another example.

*Delta or Δ.* The term delta is used to indicate that a double bond is present in a compound which is not present in the parent compound from which it is named. Thus prednisone is sometimes called deltacortisone or  $\Delta^1$  cortisone. The superscript <sup>1</sup> in the last name shows that the double bond which must be introduced into the cortisone molecule in order to change it into prednisone occurs after carbon atom number one.

*Des or De* before the name of a substituent means that this substituent is to be omitted from the parent compound in the structure of the derivative. Examples are desoxyephedrine (which has the same structure as ephedrine less the hydroxyl group) and deoxycorticosterone. It is to be noted that deoxy, or desoxy mean removal of an OH group. The term dehydroxy is not used. *De oxo* indicates the omission of a ketonic oxygen atom.

*Epi.* The prefix *epi* is used to indicate inversion of configuration about a single carbon atom. For example, *epi* androsterone is identical with androsterone apart from the configuration of the carbon atom bearing the hydroxyl group.

*Hom or Homq.* The prefix *homo* is used to indicate a compound possessing one more carbon atom than the parent molecule. The term is frequently used in connection with steroids possessing a six-membered ring D in place of the usual five-membered ring, and such compounds are known as D-homosteroids.

*Iso.* As well as indicating the structure of certain of the lower branched-chain alkyl radicals, the prefix *iso* is on occasion used to distinguish between two isomeric compounds, as in the case of *isomethadone* and *methadone* and the *isoure*as and the *ure*as.

*Nor.* The prefix *nor* is used to indicate that a compound contains one less carbon atom than the parent compound. Examples are *noradrenaline*, *noratropine* and *normorphine* in all of which an N-methyl group in the parent compound has been removed. The term is not restricted to N methyl groups, however, and is used in the naming of several steroids where a methyl group attached to a carbon atom has been removed.



## DILLING'S CLINICAL PHARMACOLOGY

**Pseudo or  $\psi$ .** The prefix pseudo can be used to denote isomerism as in *pseudoephedrine* which is a stereoisomer of ephedrine.

**Thio.** The prefix thio is often used to indicate the replacement of an oxygen atom in a C=O group by a sulphur atom as with the thiobarbiturates, the thioacids and the thioureas.

**Terms used to describe Optical Isomers.** Where optical isomerism is present it is necessary to specify which isomer is meant because the pharmacological action of different isomers may show considerable quantitative variation.

Where the isomer is identified solely by the direction in which it rotates the plane of polarised light the terms "*d*" and ( $\cdot\cdot$ ) or "*l*" and ( $-$ ) are used to indicate deflection to the right and to the left respectively. Thus "*d*" standing for dextro is completely equivalent to ( $+$ ); and "*l*" standing for lævo is completely equivalent to ( $-$ ): for example, *l* adrenaline or ( $-$ ) adrenaline is the isomer which rotates plane polarised light to the left. Racemic or optically inactive adrenaline is termed *dl* adrenaline or ( $\pm$ ) adrenaline.

Where the optical isomer is identified in terms of the absolute configuration of its molecule as related to D glyceraldehyde it is identified by the capital letters D or L. These are completely unrelated to the sign of rotation of the plane polarised light; in fact *l* adrenaline has the D configuration, and so to define the absolute configuration and also the sign of rotation it is written as D( $-$ ) adrenaline.









